AUSTRALIA

Patents Act 1990

IN THE MATTER OF Australian Patent Application Serial No 696764 by Human Genome Sciences, Inc.

-and-

IN THE MATTER OF Opposition thereto by Ludwig Institute for Cancer Research

THIS IS Exhibit 2 referred to in the Statutory Declaration of Kari Alitalo made before me

DATED this 27th Day of September, 2001

HELSINGIN MAISTRAATTI MAGISTRATEN I HELSINGFORS

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Witness JUKKA HEIKKILÄ
Notary Public

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STATUTORY DECLARATION

I, Peter Adrian Walton Rogers of the Department of Obstetrics and Gynaecology, Monash University, Clayton, Victoria, Australia do solemnly and sincerely declare as follows :

Introduction

1.1 I am presently working as Associate Professor and NH&MRC Principal Research Fellow with the Department of Obstetrics and Gynaecology, Monash University, Victoria Australia. Since receiving my Ph.D in 1983, I have worked substantially continuously as a scientific researcher in the U.K. and in Australia in areas of cellular and molecular biology. My research has included substantial studies and explorations in fields of microvascular function, vascular endothelial growth factors, growth of endothelial cells on vascular grafts, tumor angiogenesis, and other areas related to angiogenesis. In addition to my own research efforts and my collaborations with others, I receive numerous invitations to speak at national and international symposiums in these fields of study, I supervise post-graduate research of others, and I have authored and co-authored numerous original research articles published in peer-reviewed journals. My detailed *curriculum vitae* is attached hereto as Exhibit 1.

1.2 I have been asked by the Ludwig Institute for Cancer Research ("Ludwig Institute") to serve as a scientific expert in connection with Ludwig Institute's opposition to the issuance of a patent to Human Genome Sciences, Inc., ("HGS") based on HGS's

Australian Patent Application No. 696764. The patent application relates generally to a gene and protein for an alleged novel vascular endothelial growth factor called "Vascular Endothelial Growth Factor 2" ("VEGF2"), and thus pertains to an area of biology closely related to my research and expertise. I understand that Ludwig Institute is a named co-applicant for a different patent application directed to subject matter that may be related to "VEGF2."

1.3 Ludwig Institute has explained to me that it has retained me for the purpose of providing expert scientific analysis of Australian Patent Application No. 696764, as well as related literature, both past and contemporaneous, that may be relevant to the patentability of claims in the application. Ludwig Institute is compensating me for the time that I devote to providing my expert scientific analysis. However, I understand that I have an overriding duty to the Patent Office (and to any Australian Federal Court that should review the Patent Office decision) to provide objective scientific analysis that I believe to be truthful. I hereby affirm that, to the best of my knowledge and belief, factual statements herein are true and opinion statements herein represent my objective scientific opinion and analysis.

1.4 Throughout this declaration, I may refer to Australian Patent Application No. 696764 using various terms such as "the opposed application," "the opposed patent," "the HGS patent" or "the HGS application." All such terms should be understood to refer to the same document. References to the "specification" should be understood as references to the descriptive portion of the application, including text and figures.

1.5 At the time that I execute this declaration in the year 2000, there has been a significant body of published literature relating to the structure and functions of the gene and protein which the opposed patent refers to and I will refer to as "VEGF2." It is a complex protein that undergoes many stages of processing, and that appears to act as a growth factor for the vessels of the lymphatic system that convey lymph from tissues back into the blood. From my review of the file history of the opposed application, I observed little or no mention or appreciation by the Patent Office of any of the developments that occurred after HGS filed its priority application. I think it would

be helpful to the reader of this declaration to provide some context for the gene and protein of the invention that is not available from reading the opposed application or its file history, but that may be relevant to the issues that I discuss below in this declaration in detail.

1.5.1 There is general agreement from at least three different research groups, including HGS, that the human gene which encodes "VEGF2" encodes a polypeptide that is 419 amino acids in length. (See paragraphs 4.11 - 4.11.1, below.) Other research groups that independently discovered the "VEGF2" gene accorded it different names, such as "VEGF-C" or "VRP" (for VEGF-Related Protein). (*Id.*) Most of the investigative reports that are published in respected scientific journals use these other names, especially "VEGF-C".

1.5.1.1 The opposed application does <u>not</u> teach or suggest the complete 419 codon polynucleotide sequence or 419 amino acid polypeptide sequence. Rather, the opposed application teaches a partial sequence of about 350 codons/amino acids. The first (amino-terminal) approximately 69 codons from the full-length VEGF2 sequence are missing in the opposed application. Some time after HGS's scientists eventually discovered the additional 69 amino acids, HGS filed another series of patent applications describing this discovery. (See, *e.g.*, **Documents D44-D46.**) I understand that the Australian Patent Office very recently published its intention to grant some claims in the Australian version of this second series of patent applications. (See Australian Patent Application No. 60467/96, corresponding to Acceptance Serial No. 714484.)

1.5.1.2 It may be of interest that HGS has also filed a third series of patent applications relating to VEGF2 in 1998-1999, including a third PCT application (**Document D86**) that was published in

1999 and that appears to build upon its 1994-1995 first series of applications and 1995-1996 second series of applications.

1.5.2. All three independent research groups identified above agree that the "VEGF2" gene encodes a secreted growth factor polypeptide. All polypeptides, even polypeptides such as growth factors that are destined for extracellular secretion, are first synthesized in the cellular cytoplasm. Polypeptides that are destined for secretion generally include a short "signal peptide" at their amino terminus that is usually cleaved off but serves as a vital signal to direct the nascent protein into the cell's protein secretion apparatus. Scientific experiments reported in a respected scientific journal have indicated that the first approximately 31 amino acids from the 419 amino acid form of VEGF2 serve as a signal peptide. (See discussion in paragraph 4.11.1.2, below, and the footnote thereto.) I have seen no comparable published data evincing that the 350 amino acid partial VEGF2 sequence described in the opposed application contains any functional signal peptide, and I would be surprised if it did. It would be unusual for a gene to enode a protein having an alternative start codon and signal sequence 69 codons downstream from a first start codon and signal sequence.

1.5.3 Reports in respected scientific periodicals indicate that the processing of "VEGF2" (VEGF-C) is not limited to the mere removal of a 31 amino acid signal peptide. Rather, extensive proteolytic processing occurs at both the amino- and carboxyl-terminal ends of the polypeptide, resulting in a much smaller circulating polypeptide that has enhanced and/or new biological activities relative to the larger pre-processed forms from which it was derived. (See discussion in paragraph 4.11.1.3 below, and documents cited therein.) In its third series of VEGF2 patent applications, HGS acknowledges that such processing occurs. (See, *e.g.*, **Document D86** at p. 17, first paragraph.) However, in the opposed application filed in 1994, there is no evidence presented of complex proteolytic processing.

1.5.4 According to investigative reports published in respected scientific journals, one of the most important activities of the circulating (processed) forms of "VEGF2" (VEGF-C) is that of a growth factor for the vessels of the lymphatic system. See, *e.g.*, **Document D74** (Kukk et al, 1996). See also Jeltsch *et al.*, *Science, 276*: 1423-1425 (1997). The opposed application contains no data from any activity studies that were performed with "VEGF2" and contains no mention of this lymphatic growth factor activity.

Lack of Novelty of claims of the Opposed Application

A. **Introduction**

2.1 Through my involvement in this matter, I understand that the claims of a patent define the scope of the invention protected by the patent, and that a patent may only claim novel subject matter: patent claims that encompass subject matter that was described in other patents, publications, or other "prior art" that existed at the time of the effective filing date of the patent claim are invalid. It is my understanding that the effective filing date of a patent is the actual filing date, or sometimes the filing date of a priority application identified by the patent, if the priority application provides support for the claim. Claims that include prior art subject matter within their scope lack novelty, and are said to be "anticipated" by the prior art.

2.1.1 In this section of my declaration, I provide an analysis of whether claims in the opposed application encompass within their scope subject matter that had been described in the literature prior to 08 March 1994, the priority date of the opposed application.

2.1.2 I have reviewed the specification and claims of the opposed application, the written prosecution history of the opposed application in the Australian patent Office, and related prior art. To the extent that the scope of the claims can be determined at all,[1] I have determined that at least patent claims 1-4, 13-28, and 34-61 include within their scope subject matter that was described in the prior

[1] As set forth below in the section titled "Lack of Clarity," many of the claims lack clarity. (See paragraphs 6.1-6.11.)

art before the earliest claimed priority date (08 March 1994). My detailed analysis follows. In paragraphs 2.2-2.5 I analyze the meaning of certain terminology that appears in many of the claims. Then, in paragraphs 2.6-2.7.22, I analyze the relationship of individual claims and prior art subject matter.

B. Analysis of the meaning and scope of limitations found in the claims of the opposed application.

2.2 Several claims in the opposed application are directed to a "fragment, analogue or derivative" of a VEGF2 polypeptide (*e.g.*, claim 28) or to a polynucleotide encoding a "fragment, analogue or derivative" of a VEGF2 polypeptide (*e.g.*, claims 1-4, 21).[2] According to the specification, fragments, derivatives, or analogues may be VEGF2 polypeptides modified such that one or more of the amino acid residues of VEGF2 are substituted with conserved or non-conserved amino acid residues, and/or ones in which additional amino acids are fused to the mature polypeptide. (See, *e.g.*, opposed application at pp. 9-10.) Also, polypeptides resulting from deletion of amino acids would still fall within the commonly accepted definition of "fragment, analogue, or derivative." (See also opposed application at page 7, discussing "deletion variants, substitution variants, and addition or insertion variants.")

2.2.1 The prior art discloses polypeptides (*e.g.*, Vascular Endothelial Growth Factor (VEGF), Placenta Growth Factor (PlGF), and Platelet Derived Growth Factor (PDGF)) having some amino acids that are identical to the VEGF2 that is taught in the specification and some amino acids that are different, as well as polynucleotides encoding such polypeptides. (See, e.g., Documents D5 (p. 696 Fig. 1 and p. 697 Fig. 2), D6 (p. 523 Fig. 1 and p. 524 Fig. 3), D12, D18, D19 (p. 9269 Fig. 1 and 2), and D34-D36.) The relationship between the amino acid sequences of VEGF2 and human PDGF-a, PDGF-b, and VEGF

[2] Many of the claims are "dependent" claims because they make reference to earlier claims. From my involvement in this proceeding I understand that a claim which makes reference to an earlier claim is interpreted as including all of the limitations of the earlier claim. A claim that makes reference to multiple claims includes the limitations of any one of those other claims (in the alternative).

from the prior art is clearly evident in Figure 2A-2B of the opposed application and summarized in Figure 3.

2.2.2 By changing the "different" amino acids of VEGF2 (by fragmenting, substituting with conserved or non-conserved amino acids, or adding amino acids) one can arrive at a "fragment, analogue, or derivative" of VEGF2 that has an amino acid sequence that is identical to VEGF, PlGF, or a PDGF sequence. In other words, all of the differences between the VEGF2 sequence and prior art sequences such as the human VEGF sequence can properly be characterized as modifications that involved substituting, adding, or deleting residues, the same types of modifications taught in the opposed application for making fragments, analogues, or derivatives. A substantial number of amino acid changes are required to change the VEGF2 sequence into, *e.g.*, the VEGF or PDGF sequences shown in Fig. 2A-2B. However, I find no limitation in the specification or the claims setting a maximum number of modifications that may be performed to generate a "fragment, analogue, or derivative" within the scope of the claim. Thus, polypeptide and polynucleotide claims which recite "fragment," or "analogue," or "derivative" effectively encompass prior art polypeptides and polynucleotides, including but not limited to VEGF, PlGF, and PDGFa and PDGFb polypeptides and polynucleotides.

2.3 Although the claims and specification place no limitation on the number of modifications that may be performed to generate a VEGF2 fragment, analogue, or derivative within the scope of the claim, many of the claims do place the limitation that the fragment, analogue, or derivative be an "active" one (*e.g.*, claims 1-4, 28). Other claims also include a "VEGF2 biological activity" limitation (*e.g.*, claims 13-15, 34-39). For the reasons set forth below, such "activity" limitations, to the extent their meaning can be determined at all,[3] does not exclude prior art VEGF, PlGF, or PDGF polypeptides.

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[3] I find no description whatsoever in the opposed application of any scientific experiment that demonstrates a biological activity for VEGF2. The indefiniteness of this term is discussed below in the section devoted to Lack of Clarity. (See paragraphs 6.5-6.6, below.)

2.3.1 I have carefully reviewed the entire patent specification to attempt to determine the meaning of VEGF2 "activity." The specification appears to provide no explicit definition of VEGF2 activity.

2.3.2 The Examples in the opposed application do not provide any demonstration of a VEGF2 biological activity or any guidance as to VEGF2 biological activity.

2.3.2.1 Example 1 describes a Northern blot analysis ("Northern hybridization") that the inventors performed to examine the levels of expression of VEGF2 in human tissues.[4] Northern hybridizations provide information about the presence, size, and/or quantity of RNA (a nucleic acid) in cells. The RNA may or may not encode a protein. However, a Northern hybridization provides no information about the activity of an encoded protein.

2.3.2.2 Example 2 describes "in vitro transcription and translation" of the VEGF2 cDNA. *In vitro* transcription and translation are processes of making mRNA from a DNA template ("transcription") and making protein from an RNA template ("translation"), using appropriate chemical and enzymatic reagents in a test tube ("*in vitro*"). Such experiments provide no information whatsoever about biological activity of the protein that is synthesized. The only data presented in Example 2 is the *size* of the polypeptides that were purportedly produced.

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[4] Other scientific publications relating to the VEGF2 gene, including publications of the applicant Human Genome Sciences and its scientists, suggest to me that the Experimental procedures or results from Example 1 are flawed. (See paragraphs 4.13-4.13.1, below.)

2.3.2.3 Thus, the Examples of the specification, which are the only sections that appear to describe experiments that were actually performed, provide no guidance as to the meaning of VEGF2 "activity."

2.3.3 The specification suggests many alleged "uses" for VEGF2. The listed uses include to heal wounds, including dermal ulcers, pressure sores, venous ulcers, diabetic ulcers, and abdominal wounds; to promote growth of damaged bone, periodontium, or ligament tissue; to promote endothelialization (*e.g.*, in vascular graft surgery); to diagnosis tumors, to provide cancer therapy, to treat burns and injuries where angiogenesis is desired; to repair the damage of myocardial infarction; to culture vascular endothelial cells. (See opposed application at pp. 2, 16-18.) However, the application fails to explicitly indicate the scientific basis for these alleged uses. For example, there is no description of tests that were performed to demonstrate that VEGF2 has a biological activity that is useful in such procedures, and there is no description of any assay to test for VEGF2 biological activity. The absence of working examples or descriptions of activity assays suggests to me that the patent applicants merely predicted their list of "uses" from activities and/or alleged uses of the prior art growth factors VEGF, PDGF, and/or PIGF. For example, the specification teaches that VEGF is a highly specific growth factor for endothelial cells, can promote angiogenesis, and is an important factor in wound healing; whereas PDGF is a major growth factor for connective tissue. See also **Documents D1** (p. 11260), **D12, D16, D19** (p. 9270-9271, and Fig. 7), **D36** (column 11 line 67-column 13 line 38); and **D41**. Thus, I find the meaning of VEGF2 "activity" to be ambiguous. The only aspects of the application that suggest a meaning for VEGF2 "activity" are sections that speculate VEGF2 possesses activities characteristic of other prior art members of the "VEGF family" such as VEGF and PDGF.

2.3.4 Since the functions for VEGF2 are alleged to be the same as functions for prior art growth factors (*e.g.*, VEGF, PlGF, and PDGF), it follows that

functional claim limitations directed to "VEGF2 activity" do not exclude prior art growth factor polypeptides (or polynucleotides) from the scope of the claims.

2.3.5 Based on my analysis of the meaning of VEGF2 "activity" and the meaning of "fragment, analogue, or derivative," I conclude that the definition of VEGF2 "active fragment, analogue, or derivative" includes within its scope VEGF, PDGF, and/or PlGF polypeptides, because the claims have neither a functional nor a structural limitation that excludes such polypeptides. Likewise, the genus of polynucleotides which encode an active fragment, analogue, or derivative of VEGF2 includes prior art VEGF-, PDGF-, and/or PlGF-encoding polynucleotides.

2.4 Some of the claims directed to polynucleotides or polypeptides include a limitation relating to "hybridizing" to (the complement of) a VEGF2 polynucleotide[5] or portion of a VEGF2 polynucleotide.[6] (See, *e.g.*, claims 16-20, 34-45, and other claims dependent therefrom.) However, the claim limitations directed to polynucleotide hybridization do not serve to distinguish the prior art that discloses VEGF, PlGF, or PDGF polynucleotides and/or polypeptides, because any DNA can hybridize to VEGF2 DNA if the hybridization conditions (*e.g.*, temperature and ionic strength) are sufficiently relaxed. Neither the claims nor the specification require a level of hybridization stringency that would exclude VEGF, PlGF, or PDGF polynucleotides or encoded polypeptides from the scope of the claims. (No minimum level of

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[5] These claims are generally written in groups of 2-4 claims which specify hybridization to either: SEQ ID NO: 1 or its complement, or the cDNA in ATCC Deposit No. 75698, or the complement of human VEGF-2 RNA, but which are otherwise similar to each other. (See, *e.g.*, claims 13-15 or claims 16-18.) The opposed application teaches that ATCC Deposit No. 75698 contains the sequence in SEQ ID NO: 1 (and presumably its complement, assuming a double stranded cDNA was deposited). To the extent the opposed application teaches or suggests anything about the complement of VEGF-2 RNA, it suggests that the complement of the RNA would be identical (for hybridization purposes) to the complement of SEQ ID NO: 1. Thus, I conclude that these groups of claims are attempts to claim the same subject matter with different wording. My analysis with respect to encompassing prior art is the same irrespective of which "hybridizing" sequence is recited.

[6] Claims which recite portions of VEGF2 polynucleotides (*e.g.*, claim 34 and 35 specify portions that appear to be most highly conserved between VEGF2 and prior art polypeptides and polynucleotides. The more highly conserved regions are the regions that are likely to form the most stable hybrids with prior art polynucleotides. Accordingly, my analysis of the scope of "hybridizing" limitations is applicable to the claims which recite portions as well as the claims which recite complete VEGF2 polynucleotides as the hybridization partner.

hybridization stringency is required at all.) Subparagraphs 2.4.1-2.4.3 explain these principles in greater detail.

2.4.1 Polynucleotides such as DNA comprise two strands of complementary base pairs that are held together by hydrogen bonds, thereby forming a stable "double helix." A hybridization experiment operates on the principle that dissociated single strands of base pairs (*i.e.*, denatured DNA) will readily "hybridize" to re-form double helices if they are permitted to contact each other under appropriate conditions. Thus, in a typical hybridization experiment, one studies whether a first polynucleotide (sometimes called a probe) contains a base pair sequence that is sufficiently complementary to a second sequence for the probe sequence to "hybridize" (*i.e.*, renature) to the second sequence.

2.4.2 Hybridization experiments are typically performed in buffered aqueous solutions containing controlled amounts of salts and other agents. The temperature at which perfectly matched complementary DNA strands will denature in the hybridization buffer solution is called the melting temperature of the DNA. If a hybridization experiment is performed near the melting temperature, then perfect or near-perfect matching (complementarity) of the base sequences is needed for renaturation to occur. Such hybridization conditions are termed "high stringency." However, as the temperature is lowered, chemical equilibrium begins to favor the formation of double-stranded molecules, even if the base pairing is imperfect and "mismatches" exist. In the parlance of molecular biology, imperfect matches will hybridize to each other under conditions of reduced stringency. If the temperature is dropped low enough, DNA strands whose sequences match poorly will begin to hybridize to each other.

2.4.3 Hybridization experiments are commonplace in molecular biology, and scientists can exercise considerable control over the stringency of hybridization conditions. See, *.e.g.*, Sambrook *et al.* (1989) cited below in paragraph 3.2.2. By manipulation of the hybridization temperature and the

content of the hybridization buffer (especially salt concentration and pH), a scientist can control the level of sequence similarity that is required for his probe sequence to hybridize to his target sequence. Thus, the mere fact that two sequences will hybridize to each other does not necessarily reflect sequence complementarity. One must also know the stringency of the hybridization conditions to predict the relationship of the hybridizing sequences (*i.e.*, to predict the percent mismatch that may exist).

2.5 Some of the claims to polynucleotides and polypeptides include a limitation directed to polypeptides which bind an antibody which binds (or is capable of binding) to VEGF2. (See, *e.g.*, claims 16-20 and 40-45.) At the outset, I observe that these are "theoretical" antibodies, since the opposed application fails to indicate that the inventors actually made any anti-VEGF2 antibodies. VEGF2 includes some "conserved" regions of high amino acid similarity to prior art VEGF, PDGF and PlGF polypeptides. (See, *e.g.*, boxed region of Fig. 2A). From the theoretical universe of all possible antibodies that bind to VEGF2, a molecular biologist with common general knowledge would reasonably expect that some antibodies which bind to these conserved regions (epitopes) of VEGF2 would cross-react, to some extent, with the similar regions in VEGF or PDGF or PlGF. In other words, VEGF, PDGF, and PlGF are polypeptides which bind an antibody that binds (or is capable of binding) to VEGF2. The expected antibody cross-reactivity means that the claim limitation relating to antibody binding does not exclude prior art VEGF or PDGF or PlGF polynucleotides and polypeptides from the scope of claims.

C. **Analysis of individual claims.**

2.6 In this section, I analyze whether individual claims of the opposed application encompass subject matter that was disclosed in the prior art (*e.g.*, the patent documents and journal articles that were published prior to 08 March 1994).

2.7 Each subparagraph below provides an analysis of one or more individual claims with scope sufficiently large to encompass subject matter that had been disclosed in published literature prior to 08 March 1994. The publications to which I refer do not

necessarily disclose the exact VEGF2 nucleotide or deduced amino acid sequence shown in the opposed application. However, as I explain in the preceding paragraphs and individual subparagraphs that follow, the claims at issue are not limited in scope to the exact VEGF2 sequences disclosed in the application, but are much broader:

2.7.1 Claim 1 specifies an isolated polynucleotide and includes within its scope polynucleotides that encode active fragments, analogues, or derivatives of VEGF2. As explained above in paragraphs 2.2 - 2.3.5, prior art VEGF, PDGF, and PlGF polypeptides satisfy the structural and functional requirements of the opposed application to be classified as active fragments, analogues, or derivatives of VEGF2. Thus, prior art documents that teach polynucleotides encoding VEGF, PDGF, and PlGF polypeptides anticipate claim 1. Such polynucleotides are described, *e.g.*, in **Documents D5** (p. 696 Fig. 1), **D6** (p. 523 Fig. 1), **D12**, **D18**, **D19** (p. 9269 Fig. 1), and **D34-D36**.

2.7.2 Claims 2-4 depend from claim 1 and include an additional limitation specifying that the claimed polynucleotide is DNA, RNA, or genomic DNA.[7] These are all common types of polynucleotides that are specifically exemplified or suggested in the prior art that discloses VEGF, PDGF, and/or PlGF. See, *e.g.*, **Documents D5** (p. 696-698 and Figs. 1 & 3), **D6** (p. 523-526, Figs. 1, 6, 7, 8, 9, and 10), **D20** (p. 925-928 Fig. 1 and 3), and **D34** (p. 11949-11952, Figs. 1, 3, 4, 6, and 7). Thus, claims 2-4 include prior art polynucleotides within their scope.

2.7.3 Many of the cited publications teach Northern hybridization and *in situ* studies that demonstrated that RNA isolated from various sources included VEGF, PDGF, or PlGF mRNA. The RNA from these positive Northern hybridization studies is "isolated" (as defined by the opposed application at page 10) and falls within the scope of claim 3.

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[7] Because of the presence of intervening sequences, a genomic DNA is often much larger than a corresponding cDNA. It is worth noting that the opposed application only exemplifies an isolated cDNA, not an isolated VEGF2 RNA or VEGF2 genomic DNA.

2.7.4 Claims 13-15 are directed to polynucleotides that hybridize to a VEGF2-encoding polynucleotide (or the complement thereto) and that encode "a biologically active fragment of VEGF2." I observe that, during the examination period of the opposed application in the Australian Patent Office, the patent applicant argued that "biological activity may include immunogenic activity of the full length protein." (See Response paper dated 05 August 1998, filed by patent applicant.) Immunogenicity is not generally considered to be a "biological activity" of a protein, because the term "biological activity" is generally used to describe the functions of a protein in native host cells or organisms where the protein does not normally cause an antibody response. However, if "biological activity" has the broader meaning represented by the applicant to the Patent Office, then short peptide sequences of 5, 6, 7, or more residues could be considered biologically active fragments of VEGF2, because fragments of this size are generally considered large enough to elicit an immune response. (See, *e.g.*, Harlow *et al.* (1988), cited below in paragraph 3.2.2.) Both VEGF2 and the prior art human VEGF polypeptide contain an identical 7-mer sequence RCGGCCN (see Fig. 2A of the opposed application, boxed region). Polynucleotides that encode VEGF encode this RCGGCCN peptide portion of VEGF. Thus, polynucleotides that encode VEGF satisfy the "encodes VEGF2 or a biologically active fragment of VEGF2" limitation of claims 13-15, if the term "biologically active fragment" is given the meaning alleged by the patent applicant. For the reasons outlined in paragraphs 2.4-2.4.3, above, human VEGF polynucleotides also satisfy the "hybridizes" limitations of these claims. Thus, claims 13-15 are anticipated by prior art documents that disclose VEGF polynucleotides.[8] (See **Documents D6** (p. 523 Fig. 1), **D7** (p. 16319 Fig. 1), **D12**, **D18** (p. 1307 Fig. 1A and 1B), and **D34-D36**.)

2.7.5 Claims 16-18 are directed to an isolated polynucleotide which hybridizes to a VEGF2 polynucleotide and which encodes a polypeptide which binds an antibody capable of

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[8] The VEGF2 sequence taught in the opposed application also shares at least three 5-mer peptide sequences (PASCG, CVCKR, and KCACE, residues 232-236, 272-276, and 288-292 of SEQ ID NO: 2) that are identical to 5-mer sequences in a Balbiani Ring 3 protein (BR3P) of the prior art. (See Document D29 (pp. 337-340 Fig. 5).) These peptides may be sufficient to elicit an immune response, in which case prior art olynucleotides encoding BR3P also anticipate claims 13-15.

binding to VEGF2. As explained above in paragraphs 2.4-2.5, polynucleotides which encode VEGF satisfy the hybridizing limitation and encode a polypeptide (VEGF) which satisfies the antibody binding limitation. Thus, claims 16-18 are anticipated by prior art documents that disclose VEGF polynucleotides. (See **Documents D6** (p. 523 Fig. 1), **D7** (p. 16319 Fig. 1), **D12, D18** (p. 1307 Fig. 1A and 1B), and **D34-D36.**) Claim 16 also may be anticipated by prior art documents that disclose BR3P polynucleotides. (See footnote to paragraph 2.7.4.)

2.7.6 Claims 19-20 depend from claims 13-18 discussed above, and include an additional limitation specifying that the claimed polynucleotide is DNA or RNA. DNA and RNA are common types of polynucleotides that are specifically exemplified or suggested in the prior art documents that disclose VEGF. See, *e.g.*, **Documents D6** (p. 523, 524-526, Fig. 1 and 6), **D7** (p. 16318-16320, Fig. 1, 3, 5, 6, and 7), **D12, D18** (p. 1307-1308, Fig. 1A, 1B, and 2), and **D34-D36.** See also paragraphs 2.7.2-2.7.3. Thus, claims 19-20 are anticipated by prior art documents that disclose VEGF polynucleotides.

2.7.7 Claim 21 depends from claims 1-4 and 13-20 discussed above, and includes an additional limitation specifying that the polynucleotide is fused to a polynucleotide which encodes a "heterologous polypeptide." The idea of "heterologous polypeptide" was apparently intended to embrace peptides such as heterologous leader sequences known to function as a secretory signal peptide, and short tag sequences (*e.g.*, hexahistidine, hemagglutinin) to facilitate purification (see opposed application at pp. 7-8, 9-10, 14). The inclusion of such heterologous sequences in constructs for recombinant expression of proteins was well known by 1994, and is explicitly described or suggested by prior art documents relating to VEGF, PDGF, and/or PlGF. (See, *e.g.*, **Documents D35** (column 25 lines 4-9, column 32, lines 55-57, and column 33 line 66-column 34 line 4) and **D36** (column 36 lines 29-34).) Thus, the scope of claim 21 embraces prior art teachings related to VEGF, PDGF, and/or PIGF.

2.7.8 Claims 22-27 are directed to a vector containing the polynucleotide of claim 1-21, a host cell engineered with the vector, a method of producing polypeptides encoded by

polynucleotides using the host cell, and a method of producing such host cells. The additional limitations of these claims are all directed to conventional molecular biology materials and methods that are used to express polypeptides encoded by polynucleotides. (See documents cited in paragraph 3.2.2, below.) Such vectors, host cells, and methods are explicitly disclosed or suggested by prior art documents that relate to VEGF, PDGF, and/or PlGF. (See, *e.g.*, **Documents D6** (p. 522), **D18** (pp. 1306 and 1308), and **D36** (column 2 lines 14-17, column 15, line 66, to column 20, line 5; Example 8; Example 13; and Fig. 10, described at column 4, line 20-25).) Thus, the additional limitations of claims 22-27 are also taught by the prior art that anticipates claims 1-4 and 13-20, rendering claims 22-27 anticipated.[9]

2.7.9 Claim 28 specifies an isolated or recombinant polypeptide and includes within its scope polypeptides that are active fragments, analogues, or derivatives of VEGF2. As explained above in paragraphs 2.2 - 2.3.5, prior art VEGF, PDGF, and PlGF polypeptides qualify both structurally and functionally as active fragments, analogues, or derivatives of VEGF2. Thus, the scope of claim 28 embraces prior art disclosures of VEGF, PDGF, and PlGF polypeptides. Such polypeptides are described, *e.g.*, in **Documents D5** (p. 696 Fig. 1 and p. 697 Fig. 2); **D6** (p. 523 Fig. 1 and p. 524 Fig. 3), **D12**, **D18**, **D19** (p. 9269 Fig. 1 and 2), and **D34-D36**.

2.7.10 Claim 53 is directed to a pharmaceutical composition comprising the polypeptide of claim 28 and a pharmaceutically acceptable carrier. As examples of the carrier, the specification identifies saline, buffered saline, dextrose, water, glycerol, ethanol, and combinations thereof. (See opposed application at p. 19, first paragraph.) Before the 1994 priority date, these substances were commonly used as carriers, and the prior art documents relating to VEGF, PDGF, and/or PlGF explicitly taught or suggested compositions comprising the polypeptides with such carriers. See, *e.g.*, **Documents D35** (column 11 lines 62-64), **D36** (column 12 lines 66-68) , and **D41** (column 3 line

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[9] I observe that claims 25-27 all recite "VEGF-2 polypeptide." However, since the claims apparently specify using a vector containing a polynucleotide according to any one of claims 1-21 (many of which are not limited to a particular sequence), it is not clear whether this term is intended to imply a limitation to a particular sequence. Moreover, the term is indefinite. See paragraphs 6.4-6.4.5, below.

51- column 4 line 36). Thus, the scope of claim 53 (like claim 28) embraces prior art disclosures relating to VEGF, PDGF, and/or PIGF.

2.7.11 Claims 34-39 are directed to an isolated or recombinant polypeptide which has VEGF2 biological activity and which comprises an amino acid sequence that is encoded by a polynucleotide that hybridizes to a VEGF2 polynucleotide or fragment thereof.[10] As explained above in paragraphs 2.3 - 2.3.5, VEGF, PDGF, and PIGF polypeptides described in the prior art possess "VEGF2 biological activity." As explained in paragraphs 2.4-2.4.3, the polynucleotides that encode VEGF, PDGF, and PIGF hybridize to the VEGF2 polynucleotides or fragments thereof recited in the claims. Thus, claims 34-39 are anticipated by prior art documents that disclose VEGF, PDGF, and/or PIGF polypeptides. (See, *e.g.*, **Documents D5** (p. 696 Fig. 1 and p. 697 Fig. 2), **D6** (p. 523 Fig. 1 and p. 524 Fig. 3), **D12**, **D18**, **D19** (p. 9269 Fig. 1 and 2), and **D34-D36.**)

2.7.12 Claims 40-45 are directed to an isolated or recombinant polypeptide which (a) comprises an amino acid sequence that is encoded by a polynucleotide that hybridizes to a VEGF2 polynucleotide or fragment thereof; and (b) binds an antibody which binds to VEGF2. As explained above in paragraphs 2.4-2.4.3, prior art polynucleotides that encode prior art VEGF polypeptides (or BR3P polypeptides) will hybridize to the VEGF2 polynucleotides or fragments thereof recited in the claims. As explained in paragraphs 2.5 and 2.7.4, VEGF (and probably BR3P) polypeptides described in the prior art bind antibodies which bind to VEGF2. Thus, VEGF polypeptides (and BR3P polypeptides) satisfy all of the limitations of claims 40-45, so these claims are anticipated by prior art documents that disclose VEGF (and BR3P) polypeptides. (See, *e.g.*, **Documents D6** (p. 523 Fig. 1 and p. 524 Fig. 3), **D12**, **D18** (p. 1307 Fig 1A and 1B, and p. 1308 Fig. 3), **D29** (p. 337-340 Fig. 5), and **D34-D36.**)

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[10] For the purposes of prior art analysis (both novelty and inventive step), I have assumed that ATCC Deposit No. 97149 (referred to in claims 38 and 44) contains a VEGF2 cDNA. The specification of the opposed application makes no mention whatsoever of this deposit. However, a different patent application filed by the same patent applicant (Human Genome Sciences) describes ATCC Deposit No. 97149 as containing a VEGF2 cDNA. See U.S. Patent Application Serial No. 08/465,968 filed June 6, 1995 (**Document D45**), which was amended prior to issuance to contain a cross reference to ATCC 97149 (see **Document D85**, U.S. Patent No. 5,932,540). I observe from the issued U.S. patent that ATCC 97149 was not deposited with the ATCC until May 12, 1995, more than a year *after* the filing date of the opposed application.

2.7.13 Claim 46 depends from any of claims 28-45 and further includes a limitation specifying that the polypeptide is fused to a heterologous polypeptide. For the reasons discussed above in paragraph 2.7.7 with respect to claim 21, this claim also is anticipated by the prior art. (See, *e.g.*, **Documents D35** (column 25 lines 4-9, column 32, lines 55-57, and column 33 line 66-column 34 line 4) and **D36** (column 36 lines 29-34).)

2.7.14 Claim 47 depends from any of claims 28-46 and contains a further limitation specifying that the polypeptide is in the form of a homodimer. A homodimer is an association of two identical polypeptides. The prior art relating to VEGF that anticipates one or more of claims 28-46 explicitly teaches or suggests that VEGF forms homodimers. (See, *e.g.*, **Documents D12** (p. 22), **D18** (p. 1307-1308), and **D36** (column 10, lines 15-20; column 38, lines 64-66; and column 45, lines 53-56).) In fact, the specification of the opposed application explicitly states that both PDGF-α and PDGF-β form either heterodimers or homodimers, and VEGF forms homodimers. (See p. 23, last paragraph.) Thus, claim 47 (like claim 28) embraces prior art that teaches homodimeric forms of VEGF and PDGF polypeptides.

2.7.15 Claim 48 depends from any of claims 28-46 and contains a further limitation specifying that the polypeptide is "glycosylated." Glycosylation of polypeptides (*i.e.*, the attachment of carbohydrate moieties) is commonplace in animals. The prior art relating to VEGF, PDGF, and/or PlGF that anticipates one or more of claims 28-46 explicitly teaches or suggests that these polypeptides are glycosylated. (See *e.g.*, **Documents D12** (p. 22), **D19** (p. 9267, 9269-70, Fig. 3, and Fig. 4), and **D36** (column 10 lines 20-22 and column 45 lines 11-59).) Thus, claim 48 (like claim 28) embraces prior art disclosures of glycosylated forms of VEGF, PDGF, and/or PlGF polypeptides .

2.7.16 Claim 49 is directed to an antibody capable of binding to polypeptides of any of claims 28-48. As explained in paragraphs 2.7.9-2.7.15, one or more of claims 28-48 include VEGF or PDGF or PlGF polypeptides within their scope. Consequently,

claim 49 includes within its scope prior art disclosures of antibodies raised against VEGF or PDGF or PlGF polypeptides. Such antibodies are explicitly disclosed or suggested in **Documents D6** (p. 522 and 524), **D16** (p. 250), **D19** (p. 9268, 9269, and Fig. 3), **D36** (column 14 line 9-39), and **D39** (column 5 line 64-column 6 line 33, and column 13 line 15-50). Thus, claim 49 also is anticipated by the prior art.

2.7.16.1 Claim 55 is similar to claim 49 in reciting an antibody. However, the antibody of claim 55 is an antibody produced by a process of administering a polypeptide according to claim 15 or an immunogenic fragment thereof to an animal and isolating an antibody produced by the animal. At the outset, I find claim 55 lacks clarity because claim 15 is directed to a polynucleotide, and not a polypeptide. However, for the purposes of this analysis, I shall interpret claim 55 as meaning a polypeptide encoded by a polynucleotide of claim 15. As explained above in paragraph 2.7.4, claim 15 is sufficiently broad that it includes polynucleotides that encode VEGF polypeptides. The method steps recited in claim 55 involve the most conventional and well-known method of making antibodies. (See, *e.g.*, Harlow et al., Antibodies, a Laboratory Manual, Cold Spring Harbor, New York: Cold Spring Harbor Laboratory Press (1988) cited below in paragraph 3.2.2.) Thus, I find that the antibodies of claim 55 also are anticipated by prior art relating to VEGF. See **Documents D6** (pp. 522 and 524), **D7** (pp. 16318, 16319, and Fig. 4), and **D36** (column 14 lines 9-38 and column 15, lines 31-54).

2.7.17 Claim 50 is directed to an antagonist specific for the polypeptide of any one of claims 28-48. As explained in paragraphs 2.7.9-2.7.15, one or more of these polypeptide claims include VEGF or PDGF or PlGF polypeptides within their scope. Consequently, claim 50 includes prior art disclosures of VEGF or PDGF or PlGF antagonists within its scope. Exemplary antagonists would include antibodies to

VEGF, PDGF, or PlGF.[11] Such antibodies are explicitly disclosed or suggested in **Documents D6** (pp. 522 and 524), **D16** (p. 250), **D19** (pp. 9268, 9269, and Fig. 3), and **D36** (column 14 line 39-column 15 line 30), for example. Thus, claim 50, like claim 49, embraces prior art disclosures of antibodies to VEGF, PDGF, and/or PIGF.

2.7.18 Assuming *arguendo* that VEGF2 as taught in the specification possesses any biological activity that is mediated through cell surface receptors, the claims directed to antagonists of VEGF2 are not novel over prior art disclosures of forms of the receptors to which VEGF2 could bind, but could not signal.[12] See **Document D27** (disclosing a dominant negative Flk-1 protein).

2.7.19 Claims 51 and 52 are directed to a method of treatment of a patient having need of VEGF2 or need to inhibit VEGF2 by administering an effective amount of a polypeptide according to claim 28 or an antagonist against a polypeptide of claim 28. As set forth in paragraphs 2.7.9 and 2.7.17, above, the prior art teaches polypeptides, such as VEGF, within the scope of claim 28 and also antagonists to such polypeptides. Likewise, the prior art contemplates treatment of patients with these polypeptides or antagonists. See, *e.g.*, **Documents D35** (column 10, line 63 to column 12, line 34, and Example 13), **D36** (column 11, line 67 to column 13, line 38, column 14, lines 9-38, and Example 10), and **D41**. As explained above in paragraphs 2.3-2.3.5, the opposed application alleges that the biological activities of VEGF2 are the same as the activities of prior art VEGF or PDGF polypeptides. Because of this alleged equivalence of activities taught in the opposed application, patients in need of VEGF2 (or in need of inhibiting VEGF2) would be treatable with VEGF (or with VEGF antagonists). Consequently, claims 51 and 52 embrace any prior art method of

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[11] The specification of the opposed application explicitly states that an antagonist of a polypeptide could be an antibody against the polypeptide. (See page 24, middle paragraph.)

[12] The opposed application does not teach the full length polynucleotide that encodes VEGF2 or demonstrate that VEGF2 has any "biological activity" (as that term is commonly used). However, the full-length gene from which the VEGF2 cDNA was apparently derived produces a polypeptide which binds to two receptors that were disclosed in the prior art literature. [See, *e.g.*, **Documents D26, D28,** and **D33** (describing the Flt4 and Flk1/kdr receptors); see also **Document D70** (teaching that VEGF-C is a ligand for Flt4 and kdr)] **Document D27** discloses a prior art "dominant negative" form of the Flk-1 receptor, which would presumably function as an antagonist of Flk-1-mediated VEGF2 biological activities. Thus, if VEGF2 possesses Flk-1-mediated biological activities, **Document D27** anticipates a claim to VEGF2 antagonist molecules.

treatment of patients with VEGF polypeptides that are encompassed by claim 28 (or prior art method of treatment with VEGF antagonists). In other words, the prior art documents cited above disclosed or suggested the patient population recited at the beginning of claims 51 and 52, and disclosed or suggested treating the patients with a VEGF polypeptides within the scope of claim 28 or antagonist of a VEGF polypeptide. Thus, claims 51 and 52 are not novel and/or describe what was clearly suggested by the prior art.

2.7.20 Claim 56 is directed to a fragment, analogue, or derivative of the polypeptide shown in Figure 1 having an inhibitory activity against the polypeptide of claim 28. At the outset, I observe that the opposed application fails to identify with particularity any fragment, analogue, or derivative of the Figure 1 polypeptide which has an inhibitory activity. As explained above in paragraphs 2.2 - 2.3.5 and 2.7.9, claim 28 embraces prior art polypeptides such as VEGF and PDGF's, and so does the term "fragment, analogue, or derivative of the polypeptide shown in Figure 1." The prior art taught fragments, analogues, or derivatives of VEGF/PDGF that acted as inhibitors. See, *e.g.*, **Documents D16** (p. 250) and **D36** (column 13 line 61-column 14 line 8). Thus, the prior art anticipates claim 56.

2.7.21 Claims 57-61 are omnibus claims that make reference to previous claims discussed above and also to "the Figures and/or Examples." As explained above, the claims referred to stand anticipated by prior art, such as prior art relating to VEGF and PDGF's. Since the Figures also disclose VEGF and PDGF's (See, *e.g.*, Figures 2A-2B), I find that this reference to the Figures does not serve to exclude the prior art, and claims 57-61 are also anticipated.

2.7.22 In the preceding paragraphs I cite to various documents, but these should not be considered to be the only documents that disclose the subject matter of particular claims. Other documents from **Documents D1-D41** and **D78** may disclose the same subject matter, and documents that I have not cited may disclose the same subject matter.

D. Conclusion

2.8 For the reasons outlined above, it is my opinion that all of the claims 1-4, 13-28, 34-53, and 55-61 are anticipated by the prior art.

Lack of Inventive Step

A. Introduction

3.1 Through my involvement in this matter it is my understanding that Australian patent law requires that, for an invention to be patentable, it must not only be novel over the prior art, but it must have an "inventive step" compared to the common general knowledge in Australia before the priority date and compared against each individual, publicly available document when read in light of the common general knowledge. If patent claims embrace subject matter that is a routine and obvious variation of what was taught in an individual prior art document, then the patent claim lacks inventive step.

3.2 I believe that my background and experience, as outlined above, provides me with an understanding of the common general knowledge in the fields of the invention, in Australia, at the time that the U.S. priority application and the opposed Australian (PCT) application were filed.

3.2.1 The relevant common general knowledge is the common general knowledge of an individual with an advanced degree (*e.g.*, Ph.D and/or M.D.), such as an individual being exemplified by biochemists, protein and/or polypeptide biochemists, molecular biologists, and/or cell biologists, or teams of biochemists, protein and/or polypeptide biochemists, molecular biologists, and/or cell biologists, involved in the isolation and characterization of nucleic acid sequences, automated or manual nucleic acid sequencing methods, performing and interpreting searches of publicly available databases for sequences displaying homology to a query sequence, transformation of prokaryotic and eukaryotic organisms with isolated nucleic acid sequences, expression of heterologous sequences in prokaryotic and eukaryotic host cells and/or organisms, isolation and/or characterization of factors involved in cell growth and proliferation, especially but not limited to those factors associated

with angiogenesis, in Australia at or before the priority date of the claims of the opposed application.

3.2.2 The following documents are relevant to my analysis of inventive step in that they all include disclosures concerning general methods in molecular biology and recombinant DNA and antibody technology which form part of the relevant common general knowledge in Australia at or before the priority date of the claims of the opposed application:

Sambrook, J. et al., (1989). Molecular cloning, 2nd Edn. Vols. 1-3. Cold Spring Harbour Laboratory Press, Cold Spring Harbour, New York, USA;

Watson et al. (1983). Recombinant DNA. 1st Edn. Scientific American Books, W.H. Freeman & Co. NY, USA;

Watson et al (1992). Recombinant DNA. 2nd Edn. Scientific American Books, W.H. Freeman & Co., NY, USA;

Lewin, B. (1987). Genes III. John Wiley & Sons, New York, USA;

Stryer, Lubert (1988) Biochemistry, 3rd Edn. W.H. Freeman and Company, New York, USA;

Ausubel, F.A. et al. (1994) Current Protocols in Molecular Biology, John Wiley and Sons, New York, NY, USA;

Harlow et al., Antibodies, a Laboratory Manual, Cold Spring Harbor, New York: Cold Spring Harbor Laboratory Press (1988);

Coligan, J.E. et al (1994) Current Protocols in Immunology, John Wiley and Sons, New York, NY, USA;

Peters, P. (1993) Biotechnology: A Guide to Genetic Engineering, WCB McGraw-Hill, Boston, Massachusetts, USA;

Nicholl, D.S.T. (1994) An Introduction to Genetic Engineering, Cambridge University Press;

Goeddel, D.V. (Ed) (1991) Methods in Enzymology volume 185, Gene Expression Technology, Academic Press;

Gilbert, H.F. (1992) Basic Concepts in Biochemistry: A Student's Survival Guide, McGraw-Hill, Inc.;

3.2.3 For the purposes of this section, I have also considered each of **Documents D1-D41** for what each individual document teaches in light of the common general knowledge in Australia at or before the priority date of the claims of the opposed application (as reflected, for example, in the documents cited in paragraphs 3.2.2.)

3.2.4 Likewise, I find the following documents relevant to my analysis of inventive step:

Document D79, Anderson, W.F. (1992) "Human Gene Therapy," *Science*, *256*:808-813;

Document D80, Friedman, T. (1992) "A Brief History of Gene Therapy," *Nat Genetics*, *2*: 93-98

Document D81, Williams, R.S. (1993) "Southwestern Internal Medicine Conference: Prospects for Gene Therapy of Ischemic Heart Disease," *Am. J. Med. Sci.*, *306*: 129-136;

Document D82, Hockel et al. (1993), "Therapeutic Angiogenesis," *Arch. Surg.*, *128*: 423-429;

Document D83, Guzman et al. (1993), "Efficient Gene Transfer Into Myocardium by Direct Injection of Adenovirus Vectors," *Circ. Res.*, *73*: 1202-1207;

3.2.5 The common general knowledge at the time of the filing of the priority application included knowledge of the following:

nucleotide and protein sequence information regarding vascular endothelial growth factor (VEGF), platelet derived growth factors (PDGFs, such as PDGF-α and PDGF-β) and placenta growth factor (PlGF); knowledge of the biological activities of these proteins; and sequence alignments to identify conserved regions of these proteins;

vectors and host cells suitable for recombinant expression of mammalian proteins, and methodologies for producing such proteins recombinantly;

materials and methods for generating short peptides of any desired amino acid sequence synthetically;

materials and methods for selectively altering one or more codons of a gene and using the altered gene to produce proteins with one or more amino acids selectively changed or deleted or added;

materials and methods for making polyclonal and monoclonal antibodies against virtually any purified antigen, including but not limited to purified proteins, recombinant proteins, and synthetic peptides; and

materials and methods for performing gene therapy on human cells or in humans.

3.2.6 The common general knowledge before 1994 included an appreciation that molecules having the apparent biological activities of VEGF or PDGF or PlGF would be useful to treat certain diseases and conditions, and that other diseases and conditions might be effectively treated by inhibiting the apparent biological activities of VEGF or PDGF or PlGF. See, *e.g.*, **Documents D16** (p. 250), and **D36** (column 11, line 67, to column 15, line 54).

3.3 This section of my declaration should be viewed as an extension of the previous section relating to novelty, which is incorporated herein by reference. In the novelty section I focused on what had actually been disclosed in individual prior art documents, such as **Documents D1-D41** and **D78**. In this section, I have been asked to focus not only on what was explicitly disclosed in such documents, but also what was clearly suggested by individual documents to a worker possessed with the

common general knowledge.[13] In addition to (or in the alternative to) lacking novelty, it is my opinion that at least patent claims 1-4, 11, 19-28, 32, 40, 46-54, and 56-61 lack inventive step because they encompass what would have been considered obvious or routine from individual documents and/or from the common general knowledge. My detailed analysis follows:

B. Analysis of Inventive Step and the claims of the Opposed Application.

3.4 Claims 1-2, 28, 56-57, and 61, at least, attempt to define an invention pertaining to fragments, analogues, and/or derivatives of VEGF2 that possess VEGF2 activity (or polynucleotides encoding them). As explained in the following subparagraphs, these claims include within their scope subject matter that was obvious or routine from individual prior art documents.

3.4.1 Many individual prior art documents disclosed or suggest one or more of the prior art growth factor genes and proteins (*e.g.*, VEGF, PDGF, and PlGF), or fragments, analogues or derivatives of these prior art growth factors. (See, *e.g.*, documents cited in paragraphs 2.3.3 and 2.7.1-2.7.22.).

3.4.2. As explained in detail above in paragraphs 2.2-2.3.5, the specification of the opposed application fails to distinguish the theoretical structure or activity of VEGF2 fragments, analogues, or derivatives possessing VEGF2 activity from the structure and activity of the prior art growth factors VEGF, PDGF, or PlGF, or fragments, analogues or derivatives of these growth factors that were disclosed or suggested in the prior art. The specification also fails to provide any teaching or exemplification of active fragments, analogues, and/or derivatives of VEGF2. The absence of particular examples and the absence of characteristics to distinguish active VEGF2 fragments, analogues, and derivatives from prior art VEGF, PDGF, PlGF, and fragments thereof lead me to conclude that there is no invention in the opposed application with respect

[13] In the above section relating to novelty, I sometimes discussed what various documents suggested to the reader. Such discussions should be understood as relating to lack of inventive step.

to "active fragments, analogues, and/or derivatives" of the VEGF2 gene or protein. In other words, I find that VEGF, PDGF, and PlGF, and active fragments, analogues, and/or derivatives thereof were known or suggested by individual prior art documents cited above in paragraphs 2.3.3 and 2.7.1-2.7.22, and that such molecules are within the scope of claims 1-4, 28, 56-57, and 61.

3.4.3 Claims 3 and 4 specify an isolated RNA polynucleotide and an isolated genomic DNA polynucleotide, respectively. As explained above, the scope of claims 3 and 4 are sufficiently broad to encompass isolated RNA/genomic DNA polynucleotides that encode not only VEGF2, but also ones that encode VEGF or PDGF or PlGF. (See, *e.g.*, paragraphs 2.2-2.3.5 and 2.7.1-2.7.2, above.) To the extent that the prior art had not explicitly isolated RNA or genomic DNA encoding any of these three polypeptides, it is my opinion that such RNA and genomic DNA was no more than routine variation over prior art disclosures of cDNAs encoding these three polypeptides. Thus, I find that the subject matter of claims 3 and 4 is nothing more than a routine and obvious extension of individual documents that taught a cDNA polynucleotide that encodes VEGF or PDGF or PlGF. See, *e.g.*, **Documents D5** (p.696, Fig.1), **D6** (p.523, Fig. 1), **D12** (pp. 20-21), **D18** (pp. 1307-1308), **D19** (p.9269, Fig. 1), **D34** (pp. 11948-11950), **D35** (col. 27, line 45, to col. 29, line 24, and Fig. 7), and **D36** (col. 31, line 20, to col. 32, line 68, and Fig. 7).[14]

3.4.4 Claim 21 depends from claim 1 (and other claims) and further specifies that the polynucleotide of claim 1 is fused to a polynucleotide which encodes a

[14] The opposed application does not actually teach a VEGF2 genomic DNA. Thus, if genomic DNAs for growth factors like VEGF or VEGF2 are not obvious and routine variations from teachings of cDNAs, then it is my opinion that the opposed application fails to provide the public with a disclosure that is insufficient to obtain a genomic VEGF2 DNA as recited in claim 4.

heterologous polypeptide. Similarly, claim 46 depends from claim 28 (and other claims) and further specifies that the recombinant polypeptide of claim 28 is fused to a heterologous polypeptide. I explain above that claims 1 and 28 are sufficiently broad to embrace polynucleotides and polypeptides of prior art growth factors such as VEGF, PDGF, or PlGF. (See, *e.g.*, paragraphs 2.7.1 and 2.7.9, above.) It is my opinion that, prior to the priority date of the opposed application, it was routine to fuse a protein-encoding polynucleotide to heterologous polynucleotide sequences which encoded heterologous polypeptides such as epitopes to facilitate purification. [See, *e.g.*, documents cited in paragraphs 2.7.7 and 3.2.2, above] Thus, the subject matter of claims 21 and 46 is merely a routine and obvious extension over individual prior art documents which taught a cDNA and deduced amino acid sequence for VEGF or PDGF or PIGF. See, *e.g.*, **Documents D5** (p.696, Fig.1), **D6** (p.523, Fig. 1), **D12** (pp. 20-21), **D18** (pp. 1307-1308), **D19** (p.9269, Fig. 1), **D34** (pp. 11948-11950), **D35** (col. 27, line 45, to col. 29, line 24, and Fig. 7), and **D36** (col. 31, line 20, to col. 32, line 68, and Fig. 7).

3.4.5 Claims 47 and 48 depend from claim 28 (as well as other claims) and further include limitations relating to polypeptides that form a homodimer or that are glycosylated. For the reasons specified in paragraphs 2.7.14-2.7.15, it is my opinion that these limitations merely reflect the prior art knowledge that VEGF and/or PDGF polypeptides formed homodimers and were glycosylated. Therefore, the subject matter of claims 47-48 is nothing more than a routine and obvious extension of the prior art documents cited in paragraphs 2.7.14-2.7.15.

3.4.6 Claim 49 specifies an antibody that is capable of binding to a polypeptide according to claim 28 (or other claims). For the reasons set forth in paragraph 2.7.16, I find that the subject matter of claim 49 is disclosed in or is no more than an obvious and routine extension of the individual **Documents D6, D16, D19, D36,** and **D39** cited therein. Similarly, the subject matter of claim 50, directed to an antagonist, is disclosed in or is no

more than an obvious and routine extension of the teachings of individual documents identified and discussed in paragraphs 2.7.16-2.7.17.

3.4.7 Claim 53 recites a pharmaceutical composition comprising the polypeptide of claim 28 and a pharmaceutically acceptable carrier. For the reasons set forth above in paragraph 2.7.10, the subject matter of this claim is disclosed in or is no more than an obvious and routine extension of the teachings of individual documents cited therein.

3.5 Certain claims (*e.g.*, claims 11, 32, and 40, and claims dependent therefrom) encompass polypeptides (or encoding polynucleotides) that differ from prior art VEGF, PDGF, and/or PlGF polypeptides (and polynucleotides) by as few as three or four amino acids (or codons).[15] Before the 1994 priority date, it was routine for the skilled addressee to introduce 3-4 amino acid (or codon) changes into a polypeptide (or polynucleotide) sequence, *e.g.*, using procedures such as site-directed mutagenesis. [See, *e.g.*, documents cited in paragraph 3.2.2, above.] Thus, in the absence of a noteworthy change in properties that results from the change in 3-4 amino acids, I would conclude that there is nothing inventive in the molecules of claims 11, 32, and 40 over the prior art VEGF, PDGF, and/or PlGF cDNA and polypeptide molecules. (In the absence of a change in function or properties, the molecules of claims 11, 32, and 40 would represent no more than a minor change in structure with no changes in function.) I have reviewed the opposed application and find that the inventors have not alleged or demonstrated that the three or four specified alterations to native PDGF or VEGF cause the encoded proteins to differ in

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[15] These claims recite a short segment of the VEGF2 gene or protein (*e.g.*, residues 61-74 of SEQ ID NO: 2) that contains several residues which are highly conserved when compared to VEGF or PDGF polypeptides. (See boxed portion of Fig. 2A in the opposed application.) These claims also employ the term "comprising" to define their metes and bounds. As I understand the intended meaning of the term "comprising" (patent at page 29, last paragraph), the claim would include the recited core residues 61-74 of SEQ ID NO: 2, in combination with any other residues, including but not limited to all of the upstream and downstream residues of VEGF or PDGF as shown in Figure 2. Thus, by way of example, claim 11 would appear to include a polynucleotide that encoded a polypeptide identical to VEGF, except that codons for the sequence PSCVPLMRCGGCCN in the middle of VEGF would be replaced by codons for the sequence PPCVSVYRCGGCCN, a net change of four codons in the entire VEGF molecule (changes emphasized). A net change of only three codons is needed to arrive at the PDGFa sequence shown in the top line of Fig. 2A of the opposed application.

activity or function from native VEGF, PDGF, and/or PlGF. Thus, I find that polynucleotides and polypeptides within the scope of claims 11, 32, and 40 represent nothing more than routine modifications of individual prior art documents which teach VEGF or PDGF cDNA and deduced amino acid sequences, which modifications result in no reported or apparent unexpected properties. See, *e.g.*, **Documents D5** (p.696, Fig.1), **D6** (p.523, Fig. 1), **D12** (pp. 20-21), **D18** (pp. 1307-1308), **D34** (pp. 11948-11950), **D35** (col. 27, line 45, to col. 29, line 24, and Fig. 7), and **D36** (col. 31, line 20, to col. 32, line 68, and Fig. 7).

3.5.1 Claims 19 and 20 depend from claim 11 and specify DNA and RNA polynucleotides, *i.e.*, the two common forms of polynucleotides. The art cited in paragraph 3.5.1 discloses cDNAs, which are DNA. Thus, the subject matter of claim 19 is obvious for the same reasons (set forth in 3.5.1) that the subject matter of claim 11 is obvious. As explained in paragraph 3.4.3, RNA polynucleotides represent a routine variation over DNA polynucleotides. Therefore, because the subject matter of claim 11 is no more than an obvious and routine extension of individual prior art documents, dependent claim 20 also represents no more than an obvious and routine extension of individual prior art documents.

3.6 In the section above pertaining to novelty, I explain that many of the claims which recite polynucleotides or polypeptides are sufficiently broad to encompass VEGF or PDGF or PlGF polynucleotides or polypeptides. I also explain that dependent claims which specify vectors, host cells, methods of producing polypeptides, antibodies, antagonists, and the like (*e.g.*, at least claims 22-27 and 58-60) would include within their scope vectors and host cells that include VEGF or PDGF or PlGF polynucleotides; methods of producing VEGF or PDGF or PlGF polypeptides; and antibodies and antagonists to VEGF or PDGF or PlGF. It was a common practice before the priority date of the opposed application to insert a protein-encoding polynucleotide into a vector and insert the vector into a host cell to attempt to amplify the polynucleotide and/or to recombinantly produce the encoded

polypeptide.[16] [See, *e.g.*, documents cited in paragraph 3.2.2, above.] Thus, even if no single prior art document discloses a vector or host cell containing a VEGF or PDGF or PlGF polynucleotide, or a method of recombinant production, I believe that such materials and methods were no more than routine and obvious variations of the individual documents which disclosed VEGF or PDGF or PlGF DNA or deduced amino acid sequences. Thus, I find that the subject matter of claims 22-27 and 58-60 of the opposed application is disclosed in or is no more than an obvious and routine extension of documents which taught a VEGF or PDGF or PlGF polynucleotide or deduced amino acid sequence. See, *e.g.*, **Documents D5** (p.696, Fig.1), **D6** (p.523, Fig. 1), **D12** (pp. 20-21), **D18** (pp. 1307-1308), **D19** (p.9269, Fig. 1), **D34** (pp. 11948-11950), **D35** (col. 27, line 45, to col. 29, line 24, and Fig. 7), and **D36** (col. 31, line 20, to col. 32, line 68, and Fig. 7).

3.7 The common general knowledge and/or the teachings of individual documents before 1994 included an appreciation that molecules having the apparent biological activities of VEGF or PDGF or PlGF would be useful to treat certain diseases and conditions, and that other diseases and conditions might be effectively treated by inhibiting the apparent biological activities of VEGF or PDGF or PlGF. See, *e.g.*, **Documents D16** (p.250), **D35** (column 10 line 63-column 12 line 34, and Example 13), **D36** (column 11 line 67-column 13 line 38, column 14 lines 9-38, and Example 10), and **D41**. Thus, the idea of using VEGF or PDGF or PlGF (or antagonists of these molecules) to treat a patient was within the common general knowledge before 1994, even if actual treatment had not been performed by that date. As explained in paragraph 2.7.19, above, claims 51 and 52 are sufficiently broad to include within their scope treatments using VEGF or PDGF or PlGF (or antagonists of these molecules). Thus, to the extent that such treatment was feasible, it is my opinion

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[16] The opposed application does not actually teach that recombinant, biologically active VEGF2 was actually produced. I find that the claims are obvious because they encompass prior art technology relating to VEGF and PDGF, and I express no opinion at this time whether expression of VEGF2, which apparently had never been performed, would have been routine. If expression of VEGF2 were not routine, then the description of methods of expression of polypeptides found in the opposed application may be insufficient for enabling the reader possessed with the common general knowledge to express VEGF2.

that claims 51-52, directed to such treatment, represent no more than obvious and routine extensions of individual prior art documents.[17]

3.7.1 Claim 54 is similar to claim 51 and further specifies that the therapeutic amount of polypeptide is to be administered via providing the patient with DNA encoding the polypeptide and expressing the polypeptide *in vivo*. In other words, claim 54 is apparently not directed to protein therapy, but rather is directed to "gene therapy." (See paragraph 6.8.1, below.) As explained in paragraph 2.7.19, the scope of claim 51 embraces the administration of prior art VEGF polypeptides, and thus claim 54 embraces gene therapy with prior art VEGF-encoding polynucleotides. Upon review of the opposed application, I find no description of any instances where VEGF2 gene therapy was successfully performed, or even attempted. Also, I find no teachings or guidance relating to performing gene therapy treatment that were not within the common general knowledge in Australia at the time of filing the opposed application. Thus, if obstacles existed in the prior general knowledge relating to generic methods of treatment as claimed,[18] then it is my opinion that the opposed application fails to overcome the obstacles, and therefore the application lacks a disclosure sufficient to practice methods of treatment. If no such obstacles existed, then it is my opinion that the subject matter of claim 54 is nothing more than an obvious extension of teachings of any of the individual documents cited above that disclose a VEGF polynucleotide sequence and teach that VEGF has therapeutic potential in humans.

C. Conclusion

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[17] Upon review of the opposed application, I find no teachings relating to methods of treatment that were not within the common general knowledge. Thus, if obstacles existed in the prior general knowledge relating to generic methods of treatment as claimed, then it is my opinion that the opposed application fails to overcome the obstacles, and therefore the application lacks a disclosure sufficient to practice methods of treatment. I express no opinion at this time as to whether obtacles, such as uncontrollable and undesirable side effects, existed with efforts to develop therapeutics involving VEGF or VEGF inhibitors.

[18] I express no opinion at this time as to whether obtacles, such as uncontrollable and undesirable side effects, existed with efforts to develop therapeutics involving VEGF or VEGF inhibitors.

that claims 51-52, directed to such treatment, represent no more than obvious and routine extensions of individual prior art documents.[17]

3.7.1 Claim 54 is similar to claim 51 and further specifies that the therapeutic amount of polypeptide is to be administered via providing the patient with DNA encoding the polypeptide and expressing the polypeptide *in vivo*. In other words, claim 54 is apparently not directed to protein therapy, but rather is directed to "gene therapy." (See paragraph 6.8.1, below.) As explained in paragraph 2.7.19, the scope of claim 51 embraces the administration of prior art VEGF polypeptides, and thus claim 54 embraces gene therapy with prior art VEGF-encoding polynucleotides. Upon review of the opposed application, I find no description of any instances where VEGF2 gene therapy was successfully performed, or even attempted. Also, I find no teachings or guidance relating to performing gene therapy treatment that were not within the common general knowledge in Australia at the time of filing the opposed application. Thus, if obstacles existed in the prior general knowledge relating to generic methods of treatment as claimed,[18] then it is my opinion that the opposed application fails to overcome the obstacles, and therefore the application lacks a disclosure sufficient to practice methods of treatment. If no such obstacles existed, then it is my opinion that the subject matter of claim 54 is nothing more than an obvious extension of teachings of any of the individual documents cited above that disclose a VEGF polynucleotide sequence and teach that VEGF has therapeutic potential in humans.

C. Conclusion

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[17] Upon review of the opposed application, I find no teachings relating to methods of treatment that were not within the common general knowledge. Thus, if obstacles existed in the prior general knowledge relating to generic methods of treatment as claimed, then it is my opinion that the opposed application fails to overcome the obstacles, and therefore the application lacks a disclosure sufficient to practice methods of treatment. I express no opinion at this time as to whether obtacles, such as uncontrollable and undesirable side effects, existed with efforts to develop therapeutics involving VEGF or VEGF inhibitors.

[18] I express no opinion at this time as to whether obtacles, such as uncontrollable and undesirable side effects, existed with efforts to develop therapeutics involving VEGF or VEGF inhibitors.

3.8 For the reasons outlined above, it is my opinion that at least patent claims 1-4, 11, 19-28, 32, 40, 46-54, and 56-61 encompass subject matter that is disclosed in, or represents no more than an obvious and routine extension of, subject matter taught in individual prior art documents.

Insufficiency

A. Introduction

4.1 Through my involvement in this matter, it is my understanding that Australian patent law (Section 40(2)(a)) includes a sufficiency requirement that focuses on whether a specification is sufficient to disclose the method of carrying out the invention to a person reasonably competent in the relevant field of endeavor and equipped with the common general knowledge in that field.

4.1.1 It was explained to me that the evaluation for sufficiency should take into account the common general knowledge in the art, in the sense that gaps in a patent application are not necessarily problematic when the skilled practitioner can fill the gaps with reference to the common general knowledge. At the same time, for sufficiency to exist, further inventive ingenuity should not be required to practice the claimed invention. If a competent person cannot achieve the promised result because of deficiencies in the information given in the specification, there is insufficiency.

4.1.2 I was asked to consider whether the specification of the opposed application included teachings that were commensurate in scope with the claims. It was explained to me that the directions provided in the specification must be sufficient for the execution of the invention throughout the breadth or range of the claims, and that an applicant who chooses to claim an invention broadly has an obligation to make a correspondingly wide disclosure.

4.1.3 It was also explained to me that the sufficiency of an application's disclosure is evaluated as of the application's filing date and/or priority date. If the claimed subject matter is insufficiently supported by the priority application

(*e.g.*, the priority application is non-enabling), then the claims are not entitled to the benefit of the priority date.

4.1.4 It was also explained to me that Australian law requires that a specification must describe the best method known to the applicant of performing the invention at the time of filing of the application. I was asked to consider whether there was any evidence of a violation of this requirement in the opposed application, even though such a determination is difficult without knowledge of what was in the minds of the inventors.

4.2 In this section of my declaration, I provide an analysis of whether the specification of the opposed application contains a disclosure sufficient to practice the claimed invention.

B. The Priority Date of the HGS Application.

4.3 I have reviewed the priority application (U.S. Patent Application Serial No. 08/207,550, filed 08 March 1994) cited in the opposed application to analyze whether the priority application contains sufficient subject matter upon which to fairly base claims in the opposed application. As set forth in the next paragraphs, none of claims 1-61 appear to me to be fairly based on, or enabled by, the priority application.

4.3.1 The U.S. priority application fails to identify with particularity any American Type Culture Collection biological deposit. Thus, at least claims 1, 6, 8, 14, 17, 28, 38, and 44, all of which specify a particular biological deposit that is not specified in the priority application, are not enabled by or fairly based on the priority application. (Many other claims depend from this list of claims, and thus would not be fairly based or enabled by the priority application by virtue of their dependency.)

4.3.2 The opposed application specifies that the unidentified ATCC deposit is the "controlling" description of the invention. (See specification at page 9, lines 1-6.) Thus, the failure to identify the deposit constitutes a failure to

sufficiently teach the controlling definition of the invention. Consequently, I would conclude that none of the claims are entitled to the priority date.

C. **The claimed invention is not fully and sufficiently described**

4.4 My review of the opposed application and of related documents published by the applicant and inventors *after the filing* date suggests that the specification of the opposed application fails to identify the best method known to the applicant of performing the invention. In particular, the applicant claims "VEGF2" polypeptides and polynucleotides encoding such polypeptides, but extrinsic evidence indicates that the applicant failed to disclose *the complete* VEGF2 polynucleotide and polypeptide sequences in the specification. I incorporate by cross-reference the analysis in paragraphs 4.11-4.11.3 below.

4.5 I have no means of determining when the applicants discovered the complete VEGF2 sequence, but if the applicants knew the full length VEGF2 sequence at the time of filing the opposed application, then I would conclude that the opposed application fails to describe the best method of practicing the VEGF2 polynucleotide/polypeptide invention.

4.6 It is also my opinion that the opposed application contains an inadequate characterization of VEGF2 "activity." In particular, most of the claims (*e.g.*, claims 1-10, 13-15, 19-30, 34-39, 46-51, and 53-61) attempt to define an invention by reference to VEGF2 activity, yet the specification as a whole fails to provide any evidence of VEGF2 biological activity and fails to provide any working examples to establish that the polypeptides claimed (or encoded by claimed polynucleotides) possess the alleged VEGF2 activity. (See also discussion of VEGF2 activity in paragraphs 2.3-2.3.5 and 6.5-6.6.)

4.6.1 Initially, I observe that VEGF2 (having the amino acid sequences set forth in the sequence listing or figures of the opposed application) was purportedly an unknown and uncharacterized protein prior to the filing of the opposed application. If VEGF2 were unknown, then the common general knowledge

would have been devoid of any knowledge of VEGF2 biological activities as of the applicant's filing date or priority date. It was incumbent upon the patent applicant to provide such activities. The fact that the specification fails to demonstrate any VEGF2 biological activity is especially significant in that the biological activities of VEGF2 (if any) is a concept analogous to utility: if one does not know the activities of VEGF2, one would not know how to use VEGF2 (except as a curiosity for further research).

4.6.2 I have reviewed the opposed application carefully, and it contains no demonstration (*e.g.*, data) whatsoever of a VEGF2 biological activity. Since the specification contains about 29 pages of fairly technical text, it may be helpful if I elaborate on this conclusion.

4.6.2.1 Initially, I observe that *very little of the text of the extensive specification is specifically directed to the claimed invention.* Instead, most of the specification comprises general teachings relating to recombinant DNA technology that are no more relevant to VEGF2 than to other human genes and proteins. This fact would be apparent to any reader having common general knowledge of the field of the invention, such as knowledge of general recombinant DNA technology found in the general treatises cited above in paragraph 3.2.2. The fact that most of the specification is not particularly related to VEGF2 also is evident if one performs a comparison of the opposed application to other patent applications filed by the applicant, Human Genome Sciences, on completely different inventions. Such a comparison demonstrates that the VEGF2 specification *primarily* comprises "stock" text that the applicant uses in many of its biotechnology patent

applications without regard to the particular DNA or protein that the applicant claims.[19]

4.6.2.2 The Examples section of the opposed application (pages 27-29) apparently contains data from actual scientific experiments relating specifically to VEGF2. However, as I explained above in paragraphs 2.3.2-2.3.2.3, the examples provide no guidance as to the meaning of VEGF2 "activity."

4.6.2.3 In addition to the "stock" language and the examples, neither of which have any relevance to VEGF2 biological activity, the specification of the opposed application also alleges numerous properties and/or uses for VEGF2.[20] However, there is nothing whatsoever in the application to indicate that these alleged activities are supported by any actual scientific experiments or evidence. The specification fails to demonstrate that VEGF2 possesses any of these activities or is useful for any of the alleged uses. The addressee does not know which alleged activities are correct, or which are

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[19] See, *e.g.*, **Document D47** (International Application No. PCT/US95/02950, filed on 8 March 1995 by Human Genome Sciences, Inc. (WO 95/24414), directed to "Fibroblast Growth Factor-10."); **Document D48** (U.S. Patent No. 5,633,147, filed 08 March 1994, assigned to Human Genome Sciences, Inc., directed to "Transforming Growth Factor H1"; **Document D49** (International Application No. PCT/US94/05186, filed on 10 May 1994 by Human Genome Sciences, Inc. (WO 95/19985), directed to "Hematopoietic Maturation Factor"); and **Document D50** (International Application No. PCT/US94/09484, filed on 23 August 1994, by Human Genome Sciences, Inc. (WO 96/05856), directed to "Human Chemokine Polypeptides"). All of these applications are unrelated to VEGF2 but have vast sections of descriptive text relating to recombinant DNA technology that are nearly identical (word-for-word) to sections of the opposed application.

[20] For example, the opposed application suggests at least the following properties and/or uses of VEGF2 (*e.g.*, at pp. 4 and 16-17): wound healing agent, to promote growth of damaged bone and tissue and promote endothelialization, particularly where it is necessary to re-vascularize damaged tissues, or where new capillary angiogenesis is important; diagnosis of tumors; cancer therapy (also alleged as a use of VEGF2 antagonists); identify and isolate unknown receptors of VEGF2; treat full thickness wounds such as dermal ulcers, pressure sores, venous ulcers, diabetic ulcers; treat full thickness burns; plastic surgery; induce growth of damaged bone, periodontium, or ligament tissue; treatment of periodontal disease to lead to the formation of new bone and cementum with collagen fiber ingrowths; regenerating supporting tissues of teeth, including alveolar bone, cementum, and periodontal ligament; repair of cuts, particularly abdominal wounds; promotion of endothelialization in vascular graft surgery; repair damage of myocardial infarction; in vitro culturing of vascular endothelial cells; and gene therapy.

incorrect, and it is my opinion that the unsupported and widely varied activities and uses for VEGF2 alleged in the specification would be unduly burdensome for any practitioner to test.

4.6.3 Since the specification lacks any data supporting the long list of alleged properties and uses for VEGF2, I conclude that these properties and uses ascribed to VEGF2 were based wholly on speculation that VEGF2 will possess the same activities as "prior art proteins" with which "mature VEGF2" has 22-30% amino acid identity. (See opposed application at Figs. 2-3 and descriptions thereof at pp. 4-5.) However, it is my opinion that, at the time the opposed application was filed, the skilled addressee would not have considered 22-30% amino acid identity between proteins to be predictive of biological activity of the proteins.

4.6.3.1 Initially, I observe that my opinion was apparently shared by the patent examiner who prepared the International Preliminary Examination Report (**Document D51**) for the opposed application before it entered examination in Australia. In that report, the Examiner from IPEA/US observed that the description in the opposed application provides no evidence that the disclosed protein has the alleged activity, and that based upon the limited similarity to known proteins, it cannot be predicted with any expectation of success that the full length protein has the alleged activity, much less fragments, analogues and derivatives thereof.

4.6.3.2 My conclusion also is based on scientist's experiences with other "families" of proteins that share limited amino acid sequence similarity.

4.6.3.3 For example, the Transforming Growth Factor (TGF-) superfamily of proteins possess widely divergent and sometimes opposing activities. Notwithstanding widely divergent activities, members of the TGF- superfamily often share amino acid identities of 25-50% or more, *i.e.*, levels of identity that meet or exceed the identity VEGF2 shares with VEGF or PDGF-α or -β.[21]

4.6.3.4 Insulin and Insulin-like growth factor I (IGF-1) and their respective receptors provide another example. These proteins possess significantly greater than 30% amino acid identity (*i.e.*, the level of identity between VEGF2 and VEGF), but insulin/IR are primarily involved in glucose homeostasis, whereas IGF-1/IGF-1R are primarily involved in mitogenic signaling.

4.6.3.5 Another example can be found in the proteins Epidermal Growth Factor (EGF) and Fibrillin. EGF is a growth factor that stimulates the proliferation and differentiation of many cell types, whereas fibrillin is a structural protein in microfibrils. These proteins exhibit more than 22% amino acid identity (*i.e.*, the level of identity between PDGFβ and VEGF2), but are functionally unrelated.[22]

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[21] See, *e.g.*, **Document D52** (Kingsley, D., "The TGF-β superfamily: new members, new receptors, and new genetic tests of function in different organisms," *Genes & Development*, 8:133-146 (January, 1994)); and **Document D66**, (Massague, J. "The transforming growth factor-beta family," *Annu. Rev. Cell. Biol. 6*: 597-641 (1990).

[22] See **Documents D53** (Bell et al., "Human epidermal growth factor precursor: cDNA sequence, expression in vitro and gene organization." *Nucl. Acids Res., 14(21)*: 8427-8446 (1986); **D54** (Genbank Accession No. X04571, EGF sequence); **D55** (Corson et al., "Fibrillin Binds Calcium and Is Coded by cDNAs That Reveal a Multidomain Structure and Alternatively Spliced Exons at the 5' End." *Genomics, 17*: 476-484 (1993); **D56** and **D57** (Genbank Accession Nos. X63556 and L19896, fibrillin sequences).

4.6.3.6 Another example can be found in the proteins kdr receptor tyrosine kinase and c-src. Kdr, also known as VEGFR-2, is a cell surface receptor that binds VEGF and transduces the signal of this growth factor into cells that respond to VEGF. The c-src protein is not a cell surface receptor at all. These proteins exhibit more than 27% amino acid sequence identity (*i.e.*, greater than the level of identity between VEGF2 and either PDGFα or PDGFβ), but are functionally unrelated.[23]

4.6.3.7 Another example can be found in the proteins Bcl-2 and Bax. The protein Bcl-2 (B-cell leukemia/lymphoma 2) exhibits anti-apoptotic properties through its role in such cancers as follicular lymphoma. The protein Bax is an apoptotic protein that interacts with Bcl-2 and counteracts the death repressor activity of Bcl-2. Notwithstanding their opposing activities, Bcl-2 and Bax exhibit 25% similarity at the amino acid level (*i.e.*, greater similarity than VEGF2 shares with PDGFα or PDGFβ).[24]

4.6.3.8 Another example actually can be found in VEGF and PDGFα/β. These proteins share 21-23% amino acid similarity but have distinct biological activities.[25]

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[23] See, *e.g.*, **Documents D32, D33** (Terman et al., "Identification of the kdr tyrosine kinase as a receptor for vascular endothelial cell growth factor." Biochem. Biophys, Res. Commun., 187(3):1579-1586 (September, 1992)); **D59** (Genbank Accession No. L04947 (kdr)); **D60** (Tanaka et al., "DNA Sequence Encoding the Amino-Terminal Region of the Human c-src Protein: Implications of Sequence Divergence among src-Type Kinase Oncogenes." Mol. Cell. Biol., 7(5):1978-1983 (May, 1987)); and **D61** (Genbank Accession Nos. M16237, M16243-16245, and K03212-K03218, c-src sequences.)

[24] See , *e.g.*, **Documents D62** (Tsujimoto et al., "Analysis of the structure, transcripts, and protein products of bcl-2, the gene involved in human follicular lymphoma." Proc. Natl. Acad. Sci (USA), 83:5214-5218 (July, 1986)); **D63** (Genbank Accession Nos. M13994 and M13995, Bcl-2 sequences); **D64** (Oltvai et al., "Bcl-2 Heterodimerizes In Vivo with a Conserved Homolog, Bax, That Accelerates Programed Cell Death." Cell, 74:609-619 (1993)); and **D65** (Genbank Accession Nos. L22473 and L22474, Bax sequences).

[25] See, *e.g.*, Fig. 3 of the opposed application, and **Document D36** (column 13, lines 44-49).

4.6.4 Notwithstanding the large number of activities and uses for VEGF2 that were made in the opposed application, the applicant and inventors failed to predict what appears to be one of the most important activities of VEGF2, that of a growth factor for the lymphatic system. [See, *e.g.*, **Document D74** (Kukk et al, 1996). Compare **Document D86** (WO 99/46364), a 1999 patent publication by the applicant for the opposed application, which teaches to use VEGF2 to treat lymphatic disorders.][26]

4.6.5 To summarize, the opposed application contains no demonstration of VEGF2 activity and there is no reasonable basis upon which one skilled in the art could have predicted VEGF2 activity. For these reasons, it is my opinion that the opposed application contains an inadequate description of VEGF2 "activity," a claim limitation that is prominent in most of the claims of the opposed application.

4.7 The inadequacy in teachings related to VEGF2 biological activity is compounded by the failure to teach the first approximately 69 codons of the complete VEGF2 cDNA (i.e., the VEGF2 cDNA encoding a deduced full length VEGF2 protein of 419 residues). (See paragraphs 4.11-4.11.3, below) A molecular biologist would not have expected a partial eukaryotic polynucleotide sequence to be properly expressed in eukaryotic cells if the sequence were missing the first 69 codons.[27] I have carefully reviewed the patents and journal articles of the applicant HGS that were published after the opposed application and that disclose the 419 residue VEGF2 sequence. None of those publications explicitly state that the 350 residue VEGF2 or the 326 residue "mature" VEGF2 disclosed in the opposed application have been shown to possess any biological activity.

4.8 The inadequacy in teachings related to biological activity becomes compounded with respect to claims that are not restricted to VEGF2, but are directed to fragments

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[26] See also Jeltsch *et al.*, *Science*, *276*: 1423-1425 (1997).

[27] All complex organisms including plants and animals and humans are comprised of eukaryotic cells. Bacteria and certain other single-cell organisms with no cellular nucleus are prokaryotic.

and/or analogues and/or derivatives of VEGF2 that possess VEGF2 activity. (See, *e.g.*, claims 1-4, 9-15, 19-28, 34-39, 46-48, 50-54, and 56-61.) As explained in the preceding paragraphs, the description of "VEGF2 activity" *per se* is inadequate. It is a generally accepted proposition that altering proteins by changing, adding, or deleting amino acids can change or even eliminate biological activity of the native protein. Depending on the protein, the effect of any particular change may be unpredictable. Thus, one generally needs at least an activity assay (in which a protein has a demonstrated biological activity) to determine if a modified protein (such as a fragment, analog, or derivative) has retained or lost an activity of a native (unmodified) protein. However, the opposed application does not provide a single activity assay for the skilled address to employ in order to determine if fragments, analogues, or derivatives possess VEGF2 activity. Likewise, the specification as a whole fails to provide any evidence or working examples of a fragment, analogue, or derivative of VEGF2 that retains a "VEGF2 activity." Thus, there is no evidence or guidance regarding what residues are susceptible to alteration or deletion without affecting activity. Thus, the scope of the claims is broad, the ambit of the claims is indeterminate, and the field is entirely unexplored. The failure to demonstrate a VEGF2 activity and the failure to provide a VEGF2 activity assay and the suggestion that VEGF2 may have several activities (uses) place an undue burden on the part of the skilled addressee to practice the invention.

4.9 Many of the claims are sufficiently broad to embrace polypeptide molecules having no specified biological activity whatsoever. (See, *e.g.*, at least claims 31-33, 40-45, and the claims that depend therefrom.) I have carefully reviewed the specification of the opposed application and I fail to find any indication that the applicant intended to claim polypeptides lacking biological activity. Nor do I discern an industrial applicability for such polypeptides when I read the opposed application. Thus, it is my opinion that the complete specification contains an inadequate description of the subject matter of these claims.

4.10 Many of the claims are directed to a genus of polypeptides (or to polynucleotides encoding a genus of polypeptides) defined by the ability of the polypeptides to cross-

react with antibodies that bind VEGF2. (See, *e.g.*, at least claims 16-27, 40-50, and 57-61.)[28] With respect to these claims, I observe the following:

4.10.1 I have carefully reviewed the specification of the opposed application and find no indication therein that the inventors intended all such polypeptides as part of the invention. In fact, the specification does not even identify this as a defining characteristic for a genus of polypeptides.

4.10.2 Moreover, neither the specification nor any of the claims specifies an activity or use for this broadly stated genus of polypeptides. In this regard, it is important to observe that these claims do not even specify a VEGF2 activity limitation. It is my opinion that many such polypeptides could be synthesized in the laboratory that would satisfy the claim limitations but that would have no useful biological activity, and no practical utility whatsoever.

4.10.3 Moreover, even though the claims attempt to define a polynucleotide (or polypeptide) invention with respect to an antibody, the specification fails to disclose (exemplify) a single antibody to VEGF2. There is no indication in the specification that any such antibodies had been made at the time that the application was filed. Nor do I find any description in the application of which portions of VEGF2 are antigenic. In other words, there is no description of the portions of VEGF2 to which antibodies would bind if VEGF2 were administered to an animal as an antigen. There is no description of studies which characterize the molecules to which VEGF2 antibodies would bind.

4.10.4 Moreover, the specification fails to disclose a single polypeptide that binds an antibody which binds VEGF2 (other than VEGF2 itself, having the

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[28] The claims generally also include a limitation relating to polynucleotide hybridization. As I explain elsewhere (*e.g.*, in paragraphs 2.4-2.4.3), this hybridization language fails to narrow the claims due to a lack of any limitation relating to stringency of hybridization conditions.

particular VEGF2 amino acid sequences disclosed in the application, and the admitted prior art polypeptides shown in Figure 2).

4.10.5 Moreover, the specification fails to describe any characteristics of polypeptides, other than VEGF2, that bind an antibody which binds VEGF2. The skilled addressee understands that an ability of two polypeptides to cross-react with the same antibody is indicative only of the fact that the polypeptides share a small region (epitope) of similar structure. Nothing can be concluded as to overall structural similarity or functional similarity of two polypeptides merely from the fact that a theoretical antibody can bind both polypeptides by virtue of a common epitope.

4.10.6 For these reasons, it is my opinion that the opposed application contains an inadequate description of the subject matter of claims 16-27, 40-50, and 57-61 and an inadequate description of how to use it.

4.11 Another inadequacy becomes apparent when one considers the true nature of the gene from which the VEGF2 described in the opposed application was produced. As explained in the following subparagraphs, the opposed application contains an inadequate description of the polynucleotide and polypeptide referred to as "VEGF2".

4.11.1 In my review of scientific and patent literature, I observe that at least three different research groups have published papers and/or patent applications relating to the gene from which the VEGF2 sequence of the opposed application was derived. These groups include the owner of the opposed application, Human Genome Sciences (see, *e.g.*, **Documents D43, D44-D46, and D84-D86**), Genentech (**Documents D75** and **D84**),[29] and a group at the University of Helsinki (**Documents D71-D74**).[30]

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[29] The Genentech group calls the gene and protein VEGF related protein (VRP) instead of VEGF2.

[30] The Helsinki group calls the gene and mature protein VEGF-C instead of VEGF-2.

4.11.1.1 All three groups, *including the owner of the opposed application*, teach that the gene for VEGF2 encodes a protein of 419 amino acids.[31] The opposed application fails to teach the complete gene and protein sequence for the 419 amino acids. Rather, the opposed application teaches that VEGF2 is a polypeptide shown in Figure 1 comprising 350 amino acid residues of which approximately the first 24 amino acids represent the leader sequence which is cleaved off to yield a mature VEGF2 of 326 amino acids. (See, *e.g.*, specification at p. 4, last 8 lines; and page 5, last paragraph.) The owner of the opposed application considered the additional 69 residues to be so important that it eventually filed another patent application that re-defined the terms "VEGF2" and "mature VEGF2." (See **Document D43** at p. 7, last paragraph.) However, by virtue of the claim term "comprising," the opposed application clearly attempts to claim the entire 419 residue sequence even though it fails to disclose the entire sequence. (See opposed application at p. 29, last paragraph.)

4.11.1.2 The approximately 69 extra amino acids that are missing in the specification of the opposed application are found at the beginning of the VEGF2 molecule. As would be expected, all three groups (in their more recent publications) teach that the VEGF2 signal peptide is found at the beginning of the 419 amino acid sequence.[32] Thus, it would appear that the signal peptide (which is crucial for directing secretion of VEGF2 in cells) is absent from the teachings of the

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[31] See **Documents D44-D45** (p. 7); **Document D46** (p. 500, Fig. 1); **Document D75** (p. 1989); **Document D72** (p. 7); and **Document D73** (p. 6).

[32] Genentech taught that the most likely cleavage was following residue 20, but suggested that cleavage might occur after residue 15 or 16. (See **Document D75** at pp. 1989-1990.) Human Genome Sciences taught that 419 residue VEGF2 has putative leader sequence of approximately 23 residues such that the mature protein comprises 396 amino acids (See Document: D43 and D44 at p. 7, last paragraph). The group in Helsinki taught that 419 residue prepo-VEGF-C had a cleavage site for the signal peptide between residues 31 and 32. (See **Document D71** at p. 3900.) When attempting to resolve conflicting definitions of the signal peptide, I observe that the Finnish group is the only group that published scientific evidence (amino terminal amino acid sequence) to support their definition of a signal peptide.

opposed application. The purported signal peptide taught in the opposed application actually is in the middle of the 419 residue VEGF2 molecule. (The first 24 residues of VEGF2 in the opposed application correspond to residues 70-93 of **Document D43**.)

4.11.1.3 From the published scientific literature that is available, it appears that the group from Finland that includes Kari Alitalo have performed the most detailed research regarding the VEGF2 gene and protein, which that group calls VEGF-C. [See, *e.g.*, **Documents D70, D71, and D74**.] The peer-reviewed journal publications of that group teach that the 419 residue form of VEGF2 is proteolytically processed to generate significantly smaller forms ("mature VEGF-C") having increased (enhanced and/or new) biological activities. (See **Document D71**, whole document.) For example, Dr. Alitalo's group teaches that when the 419 residue VEGF2 protein is processed by removal of more than 100 residues from the amino-terminus and removal of more than 190 residues from the carboxy-terminus, the resultant polypeptide having only about 125 of the 419 residues acquires a new ability to bind and activate a cell surface receptor known as VEGFR-2/Flk-1/Kdr; the resultant protein also shows increased affinity for binding and activating another receptor known as VEGFR-3/Flt-4.[33] (See, *e.g.*, **Document D71** at Fig. 10 and p. 3908, col. 2; see also **Document D73**.) Thus, it is clear from the work of others that polypeptides which could fall within the opposed application's definition of "fragment, analogue, or derivative of VEGF2" have biological activities that are different (VEGFR-2

[33] It is generally accepted that circulating growth factors exert their effects on cells through receptors, such as VEGFR-2 or VEGFR-3, expressed on cell surfaces. Thus, the ability to bind and activate receptors at physiological concentrations would generally be expected to correlate with an *in vivo* biological activity.

activation) and/or more potent (VEGFR-3 activation) than VEGF2 as taught in the opposed application.[34]

4.11.2 For the foregoing reasons, it is my opinion that the opposed application contains an inadequate description of the VEGF2 gene and protein or of any claims broader than the partial sequences actually disclosed in Figure 1. Both the larger polynucleotide and polypeptide that are originally transcribed and translated from the VEGF2 gene and the smaller, highly active mature "VEGF-C" proteins produced by cells through transcription, translation, and processing are not described in the opposed application. The scope of the current claim set appears vastly broader than what was described:

4.11.2.1 At least claims 9-12, 30-45 use "comprising" language and might be construed to encompass the 419 residue VEGF2 protein or 419 codon VEGF2 polynucleotide that is nowhere described in the specification of the opposed application, by virtue of the fact that the applicant intends "comprising" to permit the inclusion of unstated elements, such as the approximately 69 VEGF2 codons that were never taught in the application.[35]

4.11.2.2 At least claims 1, 13-15, and 28 use "fragment" language and might be construed to encompass mature VEGF-C polypeptides (and polynucleotides that encode such polypeptides) discovered by others that are nowhere described in the specification of the opposed application. Similarly, at least claims 11-12, 31-35, and 40-41 recite particular portions of VEGF2 and use the term "comprising" such

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[34] In fact, the opposed application failed to teach any receptor for VEGF2. Moreover, since VEGF2 taught in the opposed application is missing amino-terminal sequence, it is not certain that this VEGF2 would possess any biological activity.

[35] Many other claims use the terms "having" or "encoding" or "encodes." If these term are interpreted in a manner analogous to "comprising," then the full scope of the corresponding claims would be inadequately described for the same reasons set forth for claims which recite "comprising."

that the patent applicant might assert that the claims include mature VEGF-C polynucleotides and polypeptides that are not described in the opposed application.

4.11.2.3 At least claims 13-18 and 34-45 define a polynucleotide or polypeptide invention to encompass polynucleotides (or encoded polypeptides) that "hybridize" to the approximately 350 codon partial VEGF2 polynucleotide sequence in the application, or to portions thereof. Such claims might be construed to encompass the 419 codon VEGF2 polynucleotide (or encoded 419 residue VEGF2 polypeptide) that is nowhere described in the specification. These claims also might be construed to encompass polynucleotides that encode mature VEGF-C or encode other polypeptides that are undisclosed. Similarly, at least claims 16-18 and 40-45 define a polynucleotide or polypeptide invention using "binds an antibody capable of binding" language. These claims, too, might be construed to encompass the 419 codon VEGF2 polynucleotide (or encoded 419 residue VEGF2 polypeptide) or the mature VEGF-C polynucleotides or polypeptides.

4.11.2.4 At least claims 2-10, 19-27, 29-30, and 46-61 depend from the foregoing claims.

4.11.3 I understand that the Australian Patent Office very recently published its intention to grant some claims in Human Genome Sciences Australian Patent Application No. 60467/96 (**Document D44**), corresponding to Acceptance Serial Number 714484. I understand that the accepted claims include claims directed to the full length (419 codon/amino acid) VEGF2 polynucleotide and polypeptide. If one of the tests for sufficiency is that further inventive ingenuity is not required to practice a claimed invention, then Human Genome Sciences seems to have pursued a patent strategy that is incompatible with the sufficiency requirement. In the opposed

application containing only a partial VEGF2 sequence, HGS has urged that it is entitled to broad claims that encompass the full-length form of VEGF2, and then in its second application, HGS has apparently urged that inventive ingenuity was required to obtain the full length VEGF2 from the partial VEGF2 in the opposed application.

4.12 Another inadequacy becomes apparent when one considers that the owner of the opposed application might attempt to assert the allowed claims (*e.g.*, claims 1-4, 11, 28, and 31-61) against distinct genes and proteins that the inventors of the opposed application did not discover, that no one discovered until years after the opposed application was filed, and that the opposed application provides no teaching of how to make or use.

4.12.1 The molecule now known as Vascular Endothelial Growth Factor-D (VEGF-D) provides a good example of the objectionable scope of the claims. The VEGF-D gene, protein, and properties are described, for example, in **Documents D67-D69**. VEGF-D is encoded by a completely different human gene than the gene that encodes VEGF2. The VEGF-D gene and protein were not known to exist at the time that the opposed VEGF2 patent was filed. The opposed application does not disclose VEGF-D, and the existence of VEGF-D could not have been known or discerned from the opposed application. However, VEGF-D is a polypeptide whose properties include certain biological activities that are the same as, or similar to, activities alleged for VEGF2 polypeptides in the opposed application. A 325 amino acid segment of VEGF-D also shares about 40 percent amino acid identity with the ~350 amino acids of VEGF2 taught in the opposed application,[36] and there are at least ten stretches of six identical amino acids between VEGF2 and VEGF-D which might serve as common epitopes, such that certain antibodies that bind VEGF2 would also bind VEGF-D. Under at least some hybridization conditions, one would expect the VEGF2

[36] See **Document D67**, Figure 1, which contains an exemplary alignment in which VEGF2 is identified as VEGF-C (with one or two amino acid differences).

polynucleotide sequence to hybridize with the VEGF-D polynucleotide sequence.

4.12.2 To provide another example, **Document D74** discloses murine VEGF-C having about 85% amino acid identity to the protein product of the human gene corresponding to VEGF2. Murine VEGF-C shares many stretches of amino acid sequence in common with VEGF2, and one would expect that some antibodies which would bind to VEGF2 also would bind to murine VEGF-C. Likewise, the gene which encodes murine VEGF-C shares nucleotide similarity with the VEGF2 polynucleotide taught in the opposed application, so hybridization would be expected under appropriate hybridization conditions.

4.12.3 As explained in detail in the section of my declaration devoted to analysis of novelty, most claims of the opposed application are not limited to the VEGF2 sequence taught in the application. Rather, the claims attempt to define an invention with a combination of limitations directed to hybridization, antibody binding, "activity," and/or "fragment, analog, or derivatives." This language is so broad that the claims read on prior art growth factors (see paragraphs 2.2-2.8), and likewise is so broad that it reads on VEGF-D, murine VEGF-C, and other molecules that are distinct from VEGF2 and were not even discovered until years after the filing of the opposed application. Since the claims could be construed to include polypeptides that the applicant for the opposed application did not describe in the opposed application and presumably did not know existed, the scope of the claims is inadequately described.

4.13 To the extent that any features of the claimed invention are allegedly described in the Examples, I find that the opposed application to be inadequate, because the Examples contain apparent errors and omissions.

4.13.1 Example 1 of the opposed application describes Northern hybridization studies that were performed to analyze VEGF2 mRNA expression in various cells. The opposed application reports that a message of 1.6 kD was observed in Northern hybridization studies. Initially, I note that scientists do not normally report the size of mRNA in kiloDaltons (kD, a measurement of molecular weight), but rather, report such sizes in length, *e.g.*, kilobases (kb). (Compare "kD" used in specification text at p. 27 with "kb" used in Figure 5.) Next, I observe that a 1.6 kb size is inconsistent with subsequent Northern studies published by the applicant's own scientists[37] and by other researchers.[38] Third, I observe that the description of the experimental results in the text of the specification does not correspond with the results depicted in the Figure. There is no significance whatsoever ascribed to the results allegedly depicted in Figure 5. Figure 5 appears to depict hybridization of a VEGF2 probe to an mRNA species identified as 1.3 kb in size, which is inconsistent with results reported in Example 1 (Figure 4 and text) and inconsistent with other studies. Collectively, this data suggests to me that the VEGF2 probe used in the experiments reported in Example 1 of the opposed application contained sequences from a gene other than the gene which produces VEGF2, or that the Northern studies were somehow performed incorrectly.[39]

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[37] See, *e.g.*, **Document D46** at Fig. 2 and p. 500 (Hu et al., "A novel regulatory function of proteolytically cleaved VEGF-2 for vascular endothelial smooth muscle cells," *FASEB J.*, *11*: 498-504 (1997). This document, published by a named inventor and others at Human Genome Sciences, discloses Northern hybridization studies of VEGF2 in which a band of about 2.2-2.4 kb, and no band of 1.6 kb, was identified.) See also **Document D86** at Figures 14 & 15 and Example 8 (pp. 104-105).

[38] See, *e.g.*, **Document D70** at p. 292 and 296 (Fig. 7), disclosing that a probe corresponding to the gene from which the VEGF2 cDNA was derived (named VEGF-C by the authors) hybridizes to 2.4 kb and 2.0 kb mRNA species in Northern analyses, and no band of 1.6 kb. See also **Document D75** at pp. 1991-1992 and Fig. 6, disclosing that a probe corresponding to the gene from which the VEGF2 cDNA was derived (named VRP by the authors) hybridizes to a major band of about 2.4 kb and possibly a minor band of 2.2 kb in Northern hybridization studies.

[39] Claim 39 tries to define an invention by reference to "hybridizes to the complement of human VEGF-2 mRNA. The confusion about the identity of VEGF2 mRNA in this patent application renders claim 39 confusing, too.

4.13.2 Example 2 of the opposed application describes *in vitro* transcription and translation experiments, *i.e.*, attempts to generate an encoded RNA and an encoded protein from a DNA, in a test tube. The *in vitro* transcription and translation experiments, by their very nature, do not (and cannot) provide any information about VEGF2 biological activities or about the manner in which VEGF2 DNA is transcribed or translated or post-translationally-processed in living cells or organisms. The 36-38 kD and 38-40 kD polypeptides purportedly produced in Example 2 do not correspond to "mature VEGF2" as taught in the specification of the opposed application, and do not correspond in size or description to VEGF2 as later reported by the applicant[40] and others[41] in the scientific literature.

4.13.3 Moreover, the procedures described in Example 2 are not repeatable by a skilled addressee because the description is incomplete and inaccurate. The Example is incomplete in that the applicant used "VEGF primer F5" but failed to describe its sequence anywhere in the opposed application. The Example reports that the primer pair that includes primer F5 (the third primer pair) produced PCR products that encode the full polypeptide of VEGF2 but it is not clear from the description how the third primer pair can produce such products. The Example is scientifically inaccurate in that it states (and Figure 6 purportedly confirms) that the second primer pair produces a PCR product that "misses 36 amino acids coding sequence at the C-terminus of the VEGF2 polypeptide." This description is contrary to what should be produced by a primer pair that amplifies *the complete coding sequence plus 169 bp of additional 3' sequence*, as taught in Example 2.

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[40] The Hu et al. article, published by the applicant's scientists, discloses that cells produce a VEGF2 of a molecular weight significantly greater than 36-40 kD that is processed into forms that are significantly smaller than 36-40 kD. (See , **Document D46** at, *e.g.*, pp. 501-502 and Figs. 3-4.)

[41] See **Document D71** (Joukov et al.) discloses actual experiments showing that the protein product of the gene from which the VEGF2 cDNA was derived (designated VEGF-C by the authors) is expressed as polypeptides significantly greater than 36-40 kD in size and processed into polypeptides that are significantly smaller than 36-40 kD in size. (See whole document, especially Fig. 10.) See also **Document D75** (Lee et al.) predicts that the protein product of the gene from which the VEGF2 cDNA was derived (designated VRP by the authors) produces a mature polypeptide of a molecular weight of 44.8 kD, *i.e.*, greater than 36-40 kD.

Such a primer pair should result in an *in vitro* product that is not missing any amino acids from either terminus. Additionally, the description of "lanes" in Fig. 6 (which purportedly depicts results from Example 2) are inconsistent with the description of lanes in the text of the specification (at page 29) that refers to Figure 6. In addition, the "FGF control" specified in Figure 6 is not described anywhere in the text of the specification.

4.13.4 As explained above in paragraphs 2.3-2.3.5, the examples contain no data relating to VEGF2 activity or how to test for it.

4.13.5 For all of these reasons, I find that the experiments described in the Examples of the opposed application are inadequately described.

4.14 In conclusion, I am of the opinion that the opposed application contains a specification which comprises: (a) large sections of "stock" text which has no particular relevance to VEGF2 (as compared to any other gene or protein of interest); (b) predictions of biological activity and uses that are not based on any apparent experimental evidence but that are based on levels of sequence homology (22-30%) that are too low for reliable prediction; and (c) examples that are incomplete, internally inconsistent, inconsistent with later published data, and that teach nothing concerning VEGF2 biological activity. These teachings are inadequate to enable the broad scope of the claims.

Claims Not Fairly Based

A. Introduction

5.1 Through my involvement in this matter, it is my understanding that Australian patent law includes a "fair basis" requirement that focuses on whether an invention as claimed is commensurate with the disclosure in an application. It was explained to me that a claim whose scope goes beyond the disclosure of the description found in the specification (*i.e.*, a claim to an invention for which there is no real and reasonably clear disclosure) is not fairly based, and should not be granted. I was told that "fair basis" is a fact-specific inquiry that must be made on a case-by-case

basis and with consideration of the common general knowledge in the field(s) of the invention. However, I was told that certain guiding principles/inquiries are relevant to any fair basis analysis:

5.1.1 For example, one line of inquiry focuses on whether or not the alleged invention as claimed is broadly described in the specification.

5.1.2. Another inquiry is whether or not there is anything in the specification which is inconsistent with the alleged invention as claimed.

5.1.3 Another inquiry is whether or not the claim includes as a characteristic of the invention a feature as to which the specification is wholly silent.

5.1.4 Speculative claims that seek protection well beyond the consideration given by the specification in its description of the invention are properly objected to for lack of fair basis. (The concept of "consideration given by the specification" is a concept relating to the contribution that a patent applicant gives to the public through the novel teachings in a patent application, in exchange for patent rights that the applicant receives from the public.) This inquiry is particularly relevant when a claim is broad, the ambit of the claim is indeterminate, and the field claimed is largely unexplored.

5.1.5 Claims that are open-ended and so broad as to cover processes or products unrelated to the process or product actually disclosed in the specification are objectionable for lack of fair basis.

5.1.6 If there is some feature in a claim to which no reference is made in the body of the specification, or if a claim is not limited by its terms to what the patentee has stated in the body of the specification to be the embodiment of the invention, then the claim is objectionable for lack of fair basis.

5.2. I was asked to review the opposed application, the prosecution history, related documents published by the Applicant and others, and the state of the common general knowledge at the time of filing, with the preceding guidelines in mind, and provide a scientific analysis relevant to the question of whether or not claims in the opposed application are fairly based on the specification. My analysis above relating to insufficiency of the claims is relevant to this section, and is incorporated by reference. Additional particulars of my analysis follow.

B. **The claims of the opposed application are not fairly based on the specification**

5.3 Many claims (*e.g.*, claims 17, 19-27, 38, 46-50, and 57-61) attempt to define an invention by reference to an American Type Culture Collection (ATCC) biological deposit that is not identified anywhere in the specification.

5.3.1 I find mention of only one biological deposit in the specification of the opposed application, namely ATCC Accession No. 75698 (Plasmid 182,618) deposited on 4 March 1994. (See p. 5.) The application was originally filed with empty blanks instead of a cross-reference to a deposit. From reviewing the file history of the opposed application, I observe that the cross-reference to the ATCC 75698 deposit was added to the application by the applicant long after the filing date, with the Patent Office's permission.

5.3.2 Claims 38 and 44 (and thus claims 46-50 and 61 which depend therefrom) each specifies ATCC Deposit No. 97149, which is not described or referenced anywhere else in the opposed application.[42]

5.3.3 Claim 17 (and claims 19-27 and 57-60 which depend therefrom) each specifies ATCC Deposit No. 75968, which is not described or referenced anywhere else in the opposed application. (I suspect that "75968" merely

[42] The American Type Culture Collection (ATCC) is a biological depository that maintains biological materials under conditions so that they remain viable and reproducible. The ATCC accords each deposit its own accession number (reference number), and 75698 and 97149 would represent separate and distinct deposits at the ATCC.

reflects a typographical error. However, the claim as it is written literally refers to some other ATCC deposit, and not the one mentioned in the specification.)

5.3.4 These claims which attempt to define an invention by reference to a biological deposit that is nowhere mentioned in the specification are a clear example of the inclusion in a claim of a feature as to which the specification is wholly silent. Thus, there is no fair basis for these claims in the opposed application.

5.4 Many claims (*e.g.*, 1-10, 13-15, 19-30, 34-39, 46-51, and 53-61) attempt to define an invention by reference to VEGF2 "activity," yet the specification as a whole fails to provide any evidence of a VEGF2 activity.

5.4.1 I repeat by cross-reference my extensive analysis of the shortcomings of the opposed application related to "activity" earlier in this declaration, *e.g.*, in paragraphs 2.3-2.3.5 and 4.6-4.8. There, I explain that the specification lacks any demonstration of VEGF2 activity, lacks any teaching of a VEGF2 activity assay, presents only a large list of speculative uses, and fails to appreciate or predict what appears to be one of the most prominent effects of the protein produced by cells that express the gene that corresponds to VEGF2 (a lymphatic growth factor effect). Moreover, because VEGF2 taught in the opposed application is missing about 69 amino-terminal residues, it is dubious whether this VEGF2 would be expressed and secreted as an active protein by eukaryotic cells.

5.4.2 Notwithstanding the dearth of teachings, the claims apparently attempt to encompass any polypeptide that possesses any VEGF2 activity. (I repeat by cross-reference my extensive analysis of claim scope in the paragraphs above relating to lack of novelty.)

5.4.3 In my opinion, these facts clearly amount to an instance of speculative claims that seek protection well beyond the consideration given by the specification in its description of the invention. The claims are exceedingly broad, and their ambit is indeterminate due to the lack of clear meaning of "VEGF2 activity" from the specification. Almost by definition, the identification and characterization of any new gene represents a venture into a field that is largely unexplored.

5.5 Many claims (*e.g.*, claims 1-4, 9-15, 19-28, 34-39, 46-48, 50-54, and 56-61) seek protective well beyond any consideration provided in the opposed application in that they attempt to define an invention pertaining to fragments and/or analogues and/or derivatives of VEGF2 that possess VEGF2 activity (or polynucleotides encoding them). As explained in the following subparagraphs, the specification as a whole fails to provide any evidence of a VEGF2 activity, fails to provide an assay to determine if fragments possess VEGF2 activity, and fails to demonstrate a single active fragment, analogue, or derivative of VEGF2.

5.5.1 Claims which embrace fragments, analogues, or derivatives embrace a virtually infinite number of polynucleotides or polypeptides, yet the specification provides essentially no guidance as to those species which will retain "VEGF2 activity" and those species which will not. In particular, there is no guidance as to what portions of the VEGF2 molecule are required for activity and what portions are not. I repeat by cross-reference the analysis in paragraph 4.8.

5.5.2 As explained in paragraphs 2.2-2.8, these claims are so broad that they encompass prior art polynucleotides and polypeptides. Moreover, the specification provides no structural basis for distinguishing an analog or derivative of VEGF2 from an analog or derivative of VEGF, PlGF, PDGF, or other VEGF-related growth factors that were known or suggested by the prior art. Likewise, the specification provides no functional basis for

distinction, since the alleged VEGF2 activities are predicted to match activities of these prior art growth factors.

5.5.3 As explained in paragraphs 4.12-4.12.3, these claims (*e.g.*, at least claims 1-4, 11, 16-20, 22-24, 28, 31, 32, 34-45, 47-48, and 53) are so broad that they potentially encompass polypeptides and polynucleotides that are derived from different genes and that were not discovered by the applicant and were not described in the specification of the opposed application. These encompassed polypeptides and polynucleotides, like VEGF2, exist in nature and owe nothing to the teaching of the alleged invention.

5.6 Many of the claims (*e.g.*, at least claims 1-4, 11, 13-20, 28, 32, 34-45, and certain claims that depend therefrom) seek protection well beyond any consideration provided in the application to the extent that they can be interpreted to read on non-human forms of the VEGF2 polynucleotide or polypeptide or uses thereof.

5.6.1 The specification provides no structural basis for distinguishing non-human forms of VEGF2 from non-human forms of VEGF, PlGF, PDGF, or other VEGF-related growth factors that are not identified in the specification but that exist in nature. Likewise, the specification provides no functional basis for distinction, since the alleged VEGF2 activities are predicted to match activities of the prior art growth factors.

5.6.2 The specification of the opposed application explicitly states that "The VEGF2 of the present invention is of human origin." (See, p. 3, last line.) No non-human VEGF2's are disclosed.

5.6.3 Nonetheless, most or all of the claims that are not specifically limited to the alleged human sequence taught in the application might be asserted to encompass non-human polynucleotides or polypeptides due to the breadth of limitations pertaining to fragments, analogues or derivatives (see, *e.g.*,

paragraphs 2.2-2.2.2, 2.7.1, and 2.7.9) hybridization (see, *e.g.*, paragraphs 2.4-2.4.3), and antibody binding (see, *e.g.*, paragraphs 2.5 and 4.10-4.10.6).

5.7 Many claims (*e.g.*, each of claims 16-18 and 40-45, and claims depending therefrom) attempt to define an invention in terms of a polypeptide which binds an antibody capable of binding to VEGF2. The following observations are relevant to a fair basis analysis of these claims:

5.7.1 I have carefully reviewed the specification of the opposed application and find no language that supports claims reciting a polypeptide which binds an antibody capable of binding to VEGF2. There is no indication that the applicant intended to define the invention in this manner. Upon reviewing the file history, I observe that none of the original claims (as they appear in the prosecution history) attempted to define the invention in this manner.

5.7.2 I analyzed the enormous scope of these claims and the shortcomings of the specification's teachings with respect to these claims extensively above (*e.g.*, in paragraphs 2.2-2.8 and 4.10-4.10.6), which I incorporate by reference. Those paragraphs explain that the indicated claims encompass prior art and other sequences which owe nothing to the teachings of the specification.

5.7.3 Other than VEGF2 itself and prior art polypeptides, the specification fails to identify any polypeptides that bind an antibody capable of binding to VEGF2, fails to identify the properties of such polypeptides, and fails to identify an industrial applicability of such polypeptides.

5.7.4 Thus, these facts amount to another instance of broad, speculative claims that seek protection well beyond the consideration given by the specification in its description of the invention.

5.8 Many claims (*e.g.*, claims 11-12, 31-35, 40-41, and claims dependent therefrom) recite specific subsequences of the alleged VEGF2 sequences taught in the Figures or Sequence Listing. The following observations are relevant to a fair basis analysis of these claims:

5.8.1 Claims 11 and 32 define a genus of polynucleotides and a genus of polypeptides, respectively, with reference to amino acids 61-74 of SEQ ID NO: 2. Residues 61-74 of SEQ ID NO: 2 of the opposed application correspond to a sequence Pro Cys Val Ser Val Tyr Arg Cys Gly Gly Cys Cys Asn Ser. There is no mention of this specific sequence anywhere in the application. At the very bottom of page 5, the specification states that "the signature for the PDGF/VEGF family, PXCVXXXRCXGCCN, is conserved in VEGF2 (see Figure 2)." (In Figure, 2, the specified sequence is enclosed in a box.) I observe that this motif in VEGF2 corresponds to residues 60-73 of SEQ ID NO: 2, not 61-74. However, assuming for the sake of argument that the applicant intended for the claims to refer to residues 60-73, it remains my opinion that the specification evinces no intent *to claim* a genus of polypeptides using this sequence as the critical, defining limitation. The context of the quoted statement indicates that the statement is merely one of comparison of the structural-relatedness of the VEGF2 sequence to prior art sequences. There is no mention of the exact sequence *per se*, but rather, merely an observation that VEGF2 includes a segment that matches a motif (PXCVXXXRCXGCCN, where X is any amino acid). There is no more indication that the applicant intended to define a claim by this motif sequence than there is an indication that they intended to define a claim by the referent PDGF and VEGF sequences that are mentioned numerous times in the same paragraph, and that formed the original basis for discerning the motif. With respect to the known polypeptides VEGF and PDGF, I am unaware of any evidence even to this date that the specified motif sequence alone is sufficient to confer the biological activities associated with these polypeptides. It would be quite surprising to researchers in this field if this fourteen residue peptide portion

of VEGF, PDGF, or VEGF2 possessed the same biological activity as the forms of VEGF, PDGF, or VEGF2 that are truly produced in the human body, which are thought to be much larger. (See, *e.g.*, opposed application at page 2, last paragraph, stating that VEGF has four isoforms of 121, 165, 189, and 206 amino acids.)

5.8.2 Claim 34 defines an invention by nucleotides 323 to 364 of SEQ ID NO: 1, *i.e.*, that portion of SEQ ID NO: 1 that encodes the "signature" sequence referred to at the bottom of page 5 and boxed in Figure 2. Thus, the comments in paragraph 5.8.1 pertain equally to claim 34.

5.8.3 Claim 40 defines an invention by nucleotides 323 to 364 of SEQ ID NO: 1, *i.e.*, that portion of SEQ ID NO: 1 that encodes the "signature" sequence referred to at the bottom of page 5 and boxed in Figure 2. Thus, the comments in paragraph 5.8.1 pertain equally to claim 40. Moreover, the invention of claim 40 allegedly resides in any sequence that is encoded by a sequence *that hybridizes* to the indicated sequence, and that binds an antibody that binds VEGF2. As explained in paragraphs 2.4-2.5 and 4.10-4.10.6, above, these other "limitations" vastly *broaden* the scope of the claim relative to claim 32 or 34 which are themselves broad, but which do require particular short sequences. The only sequences disclosed in the opposed application that actually satisfy the limitations of claim 40 are the single VEGF2 sequence and prior art sequences such as VEGF (see paragraph 2.7.12).

5.8.4 Claims 12 and 33 define a genus of polynucleotides and a genus of polypeptides, respectively, with reference to amino acids 38-118 of SEQ ID NO: 2. Residues 38-118 of SEQ ID NO: 2 of the opposed application correspond to a sequence beginning Met Pro Arg Glu . . . and ending Cys Arg Cys Met. There is no mention of this specific sequence anywhere in the application. Near the bottom of page 5, the specification observes that "It is particularly important that all eight cysteines are conserved within all four

members of the family (see boxed areas of Figure 2)." I observe that these eight boxed cysteines (there are many other cysteines) begin at residue 37 of SEQ ID NO: 2 and extend to residue 117 of SEQ ID NO: 2, not 38-118. However, assuming for the sake of argument that the applicant intended for these claims to refer to residues 37-117, it remains my opinion that the specification evinces no intent to claim a genus of polypeptides by this sequence. The context of the quoted statement indicates that the statement is merely one of comparison of the structural-relatedness of the VEGF2 sequence to prior art sequences. There is only mention of the cysteines, and no mention of the intervening 70+ amino acids that are dispersed between the cysteines and that comprise most of the sequence between 37 and 117. There is no mention a particular VEGF2 fragment defined by the cysteines and including all of the residues between 37 and 117. There is no more indication that the applicant intended to define a claim by residues 38-118 (or 37-117) than there is an indication that they intended to define a claim by the referent PDGF and VEGF sequences that are mentioned as sharing the eight cysteines, and that formed the basis for discerning the existence of the cysteine motif.

5.8.5 Claim 35 defines an invention by nucleotides 254 to 496 of SEQ ID NO: 1, *i.e.*, that portion of SEQ ID NO: 1 beginning with the codon for the first conserved (boxed) cysteine and ending with the codon for the eighth conserved cysteine. Thus, the comments in the preceding paragraph pertain equally to claim 35.

5.8.6 Claim 41 defines an invention by nucleotides 254 to 496 of SEQ ID NO: 1, *i.e.*, that portion of SEQ ID NO: 1 beginning with the codon for the first conserved cysteine and ending with the codon for the eighth conserved cysteine. Thus, the comments in paragraph 5.8.4 pertain equally to claim 41. Moreover, the invention of claim 41 allegedly resides in any sequence that is encoded by a sequence that hybridizes to the indicated sequence, and that binds an antibody that binds VEGF2. As explained in paragraphs 2.4-

2.5 and 4.10-4.10.6, above, these other "limitations" vastly *broaden* the scope of the claim relative to claim 33 or 35 which are themselves broad, but which do require particular sequences. The only sequences disclosed in the opposed application that actually satisfy the limitations of claim 41 are the single VEGF2 sequence and prior art sequences such as VEGF (see paragraph 2.7.12).

5.8.7 Claim 31 defines a genus of polypeptides with reference to amino acids 108-121 of SEQ ID NO: 2. There is no mention of this specific sequence anywhere in the application, and thus no indication from the specification that the applicant intended to define a claim by this particular subsequence.

5.8.8 Thus, it is my opinion that the specification is wholly silent about features of these claims, or at least is silent in the sense that the specification failed to indicate that these features were intended as features defining the invention in any broad sense.

5.8.9 Moreover, these are speculative claims that seek protection well beyond the consideration given by the specification in its description of the invention. Even if we presume for argument's sake that the brief excerpts at page 5 were sufficient in a general sense to provide a description, the fact remains that there is no scientific evidence supporting the notion that the indicated subsequences (fragments) encode a polypeptide having VEGF2 activity, or that the indicated subsequences are the only sequences critical for retaining VEGF2 activity. Also, since there is no actual definition or demonstration or assay for VEGF2 activity, the opposed application fails to enable a worker possessed with the common general knowledge to test such fragments for VEGF2 activity.

5.8.10 Claim 39 doesn't recite a particular sequence, but instead recites "human VEGF-2 mRNA." As explained above in detail, Example 2, which provides the only arguable description of VEGF2 mRNA, apparently was performed

incorrectly, and VEGF2 mRNA was misidentified. (See, *e.g.*, paragraph 4.13.1. Published evidence indicates that the only mRNA that was characterized was not, in fact, a VEGF2 mRNA.) Thus, I find no support in the application for this term, either.

5.9 When one considers what is now known about VEGF2, it becomes apparent that all the claims of the opposed application seek to define a monopoly which goes beyond the consideration provided by the specification. The specification provides what is now known to be only a *partial* nucleic acid and deduced amino acid sequences of a 419 codon and residue VEGF2 cDNA and protein. (See, *e.g.*, paragraphs 4.11-4.11.2.4, above.) Although the specification provides speculation as to the biological activity of the encoded protein, it does not provide any demonstration of biological activity, and it failed to appreciate what appears to be the most significant activity of the protein that is naturally produced by cells that express the VEGF2 gene. (See, *e.g*, paragraphs 2.3-2.3.5 and 4.6-4.6.5.) Further, the person skilled in the art would not have considered it appropriate to make a sound prediction as to the activity based solely on the limited extent of homology between VEGF2 and prior art proteins. (See, *e.g.*, paragraphs 4.6.3-4.6.3.8, above.) When one considers what is now known about VEGF2, it becomes apparent that the consideration provided in the specification is little more than a partial sequence with no demonstration of activity.

5.10 At least claims 1, 9-18, 28, and 30-45, and claims dependent therefrom, of the opposed application extend beyond the subject matter of the alleged invention.

5.10.1 I repeat by cross-reference my analysis in paragraphs 4.11-4.11.3, where I explain that the specification of the opposed patent teaches only the final 350 codons/residues of the complete, 419 codon/residue VEGF2 cDNA and encoded polypeptide; it fails to teach the first 69 codons/residues, including the signal sequence at the beginning which is generally recognized as necessary for eukaryotic host cells to express and secrete a protein. However, the indicated claims could be construed to encompass (a) the full

length, 419 codon/residue VEGF2 cDNA/polypeptide with the true VEGF2 signal sequence; and/or (b) mature VEGF-C proteins discovered by others that have properties distinct from the 350 amino acid VEGF2 taught in the opposed application. Thus, the indicated claims seek a monopoly which is considerably broader than the consideration provided to the public through the teachings in the specification.

5.11 Claims 13-27, 34-50, and 57-61, at least, are not reasonably based on the material disclosed in the specification, because these claims attempt to delimit a genus of polynucleotides (or encoded polypeptides) by an ability to "hybridize" to a referent sequence. The claims which recite hybridization language do not specify hybridization conditions, and almost any polynucleotide can be made to hybridize to a given sequence under hybridization conditions of sufficiently low stringency. Given that no hybridization conditions are specified in the claims, the claims encompass prior art sequences and other sequences that owe nothing to the teaching of the specification. I repeat by cross-reference my analysis in paragraphs 2.4-2.4.3, 2.7.4-2.7.6, 2.7.11, and 4.11-4.12.3.

5.12 As I explain above in sections relating to novelty and inventive step, most or all of the claims in the opposed application include within their scope subject matter that was already known to the public, or was an obvious and routine variation of what was known to the public. Subject matter which was known or obvious to the interested scientific public cannot logically form part of the consideration *given by the patent applicant* to the public for the monopoly patent right that the applicant is seeking. Thus, I conclude that claims that are not novel or inventive, by definition, seek protection beyond the consideration given to the public by the specification. Thus, I would conclude that the claims are not reasonably based on the inventors' contributions embodied in the opposed application.

Lack of Clarity in the Claims

A. Introduction

6.1 It was explained to me that Australian patent law includes a "clarity" requirement. I understand that the claims of a patent are the portion that define the invention for which a patentee receives a monopoly, and the clarity requirement is a statutory obligation to state the invention clearly and distinctly in the claims. As part of my analysis of the opposed application, I was asked to evaluate whether the claims were clear to a skilled reader. I was told that certain guiding principles are relevant to any clarity analysis, including the following:

6.1.1 that any evaluation of clarity requires reading the claims in the context of the specification as a whole. For example, the specification may define claim terminology directly or aid in understanding claim terminology. My observations below were made while being mindful of the teachings and definitions provided in the specification of the opposed application.

6.1.2 that another aspect of clarity focuses on internal consistency, *i.e.*, whether the invention defined in the claims is the same invention as that described in the specification. For example, features emphasized in the description, especially those described as critical or essential, should be included in each claim.

6.2 In my study of the opposed application and its claims, I made several observations relevant to the issue of clarity, which I set forth below.

B. Analysis of the clarity of the claims of the opposed application.

6.3. *Lack of Clarity issues relating to the applicant's biological deposit.* The specification of the opposed application states that the controlling definition of the VEGF2 invention resides in the DNA and deduced amino acid sequence of the VEGF-2 cDNA clone deposited by the applicant with the ATCC. (See specification, paragraph bridging pages 8-9.) The specification also states that the drawings are not meant to limit the scope of the invention as encompassed by the claims. (See p. 4.) These statements raise several confusing issues.

6.3.1 Although the specification of the opposed application (as amended during prosecution) describes only a single relevant deposit (ATCC 75698), the present claims specify at least three different ATCC Accession Numbers: 75698, 75968, and 97149. Many claims (*e.g.*, each of claims 17, 19-27, 38, 46-50, and 57-61) make reference to American Type Culture Collection (ATCC) biological deposit numbers 75968 and/or 97149 that are not mentioned anywhere in the specification. (See paragraphs 5.3-5.3.4, above.) The meaning of such cross-references is unclear to a skilled reader.

6.3.2 Notwithstanding the express teaching that the drawings are not meant to limit the invention, many claims define the invention with respect to sequences depicted in Figure 1 (see. *e.g.*, at least claims 1, 5, 7, 9, 28, 29, 56-61, and claims dependent therefrom). Many other claims define the invention with respect to sequences in SEQ ID NOs: 1 or 2 (see, *e.g.*, claims 9-13, 16, 30-37, 40-43, and claims dependent therefrom). The choice to define the invention with respect to the figures or sequence listing instead of the "controlling" deposit raises issues of clarity, at least if the sequence of the deposited clone does not match the sequences in Figure 1 and/or SEQ ID NO: 1. As explained below in greater detail, inconsistencies exist amongst these sequences.

6.3.2.1 For example, position -21 of SEQ ID NO: 2 is a lysine residue (Lys). In contrast, the same position in Figs. 1A and 2A is a leucine (Leu) residue.

6.3.2.2 For example, the sequence spanning residues 274-279 of SEQ ID NO: 2 is Lys Cys Cys Leu Leu Lys. The corresponding sequence in Figs. 1C and 2B is Lys Cys Leu Leu Lys (depicted in single letter abbreviations K C L L K). Thus, SEQ ID NO: 2 includes a Cysteine that is absent from the sequence in the Figures.

6.3.2.3 The applicant performs automated sequencing which the applicant represents may have an error rate of as high as three percent,[43] suggesting that perhaps as many as 45 other sequence discrepancies may exist between the ATCC deposited clone and the sequences set forth in the sequence listing and figures of the application.[44]

6.3.3 Since the sequence in the Sequence Listing is not identical to the sequence in the figures, it must be that the DNA and deduced amino acid sequence of the deposited clone differ from those of the sequence listing, or those in Figure 1, or both. (The sequence of the deposit cannot match two different sequences.) The inconsistencies between the "controlling" sequence in the deposit and the sequences provided in the Sequence Listing and the Figures, which are supposed to match the deposit, raise questions of clarity.

6.3.4 The inconsistencies between the sequences in Figure 1 and SEQ ID NO: 2 is particularly confusing with respect to claims 9-10 and 30, and claims dependent therefrom, because these claims make reference to both the Figures and the Sequence Listing.

6.3.5 The priority application and the Australian application as filed failed to contain a proper cross-reference to the "controlling" biological deposit. Instead, there was a blank that was filled in by the applicants during prosecution, with permission from the Patent Office. Because of the blanks, references to the biological deposit in the application *as filed* would have been uninterpretable by a skilled reader.

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[43] This error rate is taught in **Documents D43 and D44,** International Patent Application No. PCT/US96/09001 (WO 96/39515) and corresponding Australian Application No. 60467/96. This later patent application is by the same applicant as the opposed application and is also directed to "VEGF2," and it specifies that sequence accuracy is only predicted to be greater than 97%.

[44] The Sequence in SEQ ID NO: 1 and Fig. 1 has more than 1500 nucleotides. Three percent of 1500 is 45.

6.3.6 Also confusing is the fact that the application, as amended, specifies at least two different plasmids as allegedly corresponding to ATCC Number 75698.

6.3.6.1 In a Notice of Entitlement (**Document D76**) dated 28 January 1997, filed with the Australian Patent Office, the Applicant listed as the controlling deposit "DNA Plasmid 161,797," allegedly deposited with the ATCC International Deposit Authority on 4 March 1994 as Deposit No. 75698.

6.3.6.2 During prosecution before the Australian Patent Office, the Applicant amended page 5 of the specification to specify the same ATCC deposit number but a different plasmid, namely "the clone deposited as ATCC Accession No. 75698 (Plasmid 182,618) on 4 March 1994." (See **Document D77**.) Thus, the identity of the controlling deposit is confusing from the entirety of the record.

6.4 Most of the claims (*e.g.*, each of claims 1-10 and 13-61) define the invention using one or more of the terms "VEGF2" or "VEGF2 polypeptide" or "VEGF-2" or "VEGF-2 polypeptide" or other like variations. As explained below, these terms are unclear.

6.4.1 "VEGF2" is a term invented by the applicants for this patent application, for which there is no prior recognized meaning in the general knowledge of the art. Likewise, the specification contains no explicit definition of "VEGF2." Because VEGF2 apparently refers to a protein and a cDNA encoding it, one might expect structural (*e.g.*, nucleotide or amino acid sequence) and/or functional definition for "VEGF2," but the application is unclear on both the structural and functional attributes that uniquely define "VEGF2."

6.4.2 The specification contains no demonstration of a biological activity that is characteristic of VEGF2. (See paragraphs 2.3-2.3.5 and 4.6-4.8, above.)

Likewise, the specification contains no description or demonstration of a biological activity that is unique and defining for VEGF2. To the extent any activity is alleged for VEGF2 (or deducible from alleged uses for VEGF2), such activity matches the activities of prior art polypeptides (see paragraphs 2.3-2.3.5 and 4.6-4.8), so the activities *per se* would not serve to distinguish VEGF2 from polypeptides that had already been described by others or from polypeptides discovered by subsequent inventors that are distinct from VEGF2.[45]

6.4.3 There appears to be no minimum particular amino acid sequence that is deemed essential for defining a VEGF2 polypeptide, as is evident from the different minimum amino acid sequences specified, *e.g.*, in claims 31-33. The VEGF2 of claim 31 (specifying only amino acids 108-121 of SEQ ID NO: 2) theoretically has *zero* amino acids in common with the VEGF2 of claim 32 (specifying only amino acids 61-74).

6.4.4 Thus, there are no clear structural or functional features for the reader to use to determine whether or not a particular polynucleotide or polypeptide is a VEGF2.

6.4.5 The skilled artisan becomes further confounded by reading the same applicant's later patent applications that teach a different VEGF2 sequence (419 amino acids) and a different "mature VEGF2" (396 amino acids). (See **Documents D43** and **D44**.)

6.5 In most of the claims (*e.g.*, each of claims 1-4, 10-15, 19-28, 34-39, 46-48, and 50-61), the concept(s) of "activity" or "biological activity" or "VEGF2 activity" is essential to the understanding of the metes and bounds of the claim. However, as explained in detail above in paragraphs 2.3-2.3.5 and 4.6-4.8, one cannot discern

[45] Moreover, to the extent that biological activity is intended by the applicant as a defining characteristic, the intended distinction between VEGF2 polypeptides (*e.g.*, as recited in claim 28) and polypeptides that have VEGF2 biological activity (*e.g.*, as recited in claim 34) becomes unclear.

what is meant by "active" or "biologically active" or "biological activity" in the context of VEGF2 polypeptides and/or fragments, analogues, or derivatives thereof. There is no definition per se of VEGF2 activity. The specification contains a large list of alleged uses for VEGF2 but does not demonstrate which uses are legitimate and which are not, and does not set forth a single biological activity that would explain why VEGF2 should be efficacious for treating the entire list of maladies and conditions that are mentioned. Moreover, the specification contains no recognition of what is apparently a prominent activity of the protein produced by the gene from which the VEGF2 cDNA was derived, namely, an activity as a lymphatic growth factor.

6.5.1 The meaning of VEGF2 "activity" becomes more confused by the prosecution history. As explained above in paragraph 2.7.4, during prosecution the patent applicant argued to the Australian Patent Office that "biological activity may include immunogenic activity of the full length protein." (See Response paper dated 05 August 1998, filed by patent applicant.) Immunogenicity is *not* generally considered to be a "biological activity" of a protein, because the term "biological activity" is generally used to describe the functions of a protein in native host cells or organisms where the protein does *not* normally cause an antibody response.

6.6 In it unclear in claims 50, 52, and 56 (and claims depending therefrom) what the applicant means by the terms "antagonist" and "inhibitory activity." The concept of antagonization or inhibition of a polypeptide relates to the blocking of the biological activity of the polypeptide. Because the definition of "activity" is unclear, the definitions of "antagonist" and "inhibitory activity" cannot be ascertained.

6.7 Many of the claims (*e.g.*, each of claims 13-27, 34-50, and 57-61) try to define the metes and bounds of the invention at least in part by hybridization terminology. The claims attempt to delimit a genus of polynucleotides (or encoded polypeptides) by an ability (or inability) of one polynucleotide to "hybridize" to a specified

polynucleotide or specified genus of polynucleotides. It is not clear what is meant in these claims by "hybridize."

6.7.1 As set forth in paragraphs 2.4 - 2.4.3, the term "hybridize" is ambiguous because it provides insufficient information to understand the relationship of two polynucleotide molecules. Under conditions of high stringency, two molecules will only hybridize if they are closely related in that their sequences are perfectly complementary or nearly so. However, under sufficiently relaxed conditions, sequences which are essentially unrelated will also hybridize to each other. None of the claims which recite "hybridize" specify the hybridization conditions, so the metes and bounds of the claims are unclear.

6.7.2 Claim 39, which tries to define an invention by reference to hybridization "to the complement of human VEGF-2 mRNA" is confusing for the reasons stated in paragraph 4.13.1, above.

6.8 *Lack of clarity with respect to method of treatment claims.* Several claims, including at least claims 51-52 and 54, are directed to methods of treating patients. There are several confusing aspects to these claims.

6.8.1 Claim 55 (and claims dependent therefrom) are ambiguous in specifying the administration of "the polypeptide of claim 15." However, claim 15 is not directed to a polypeptide at all, but rather to an isolated polynucleotide.

6.8.2 Claims 51 and 54 (and claims dependent therefrom) are ambiguous in that each apparently intends that a therapeutic amount of a polypeptide can be administered without administering any polypeptide whatsoever. In particular, claim 54 specifies that the therapeutically effective amount of polypeptide is administered by providing DNA to a patient. DNA is not a polypeptide, but a polynucleotide. Thus, even though claims 51 and 54 on their face recite administration of a polypeptide therapeutic, the applicant

apparently intends for these claims to encompass gene therapy that does not involve administering *any* of the indicated polypeptide. Thus, the meaning of "therapeutically effective amount of the polypeptide" is unclear, and apparently includes an amount equal to zero.

6.8.3 In claims 51-52 (and claims dependent therefrom), the recitations "patient having need of VEGF2" and "patient having need to inhibit VEGF2" are ambiguous. The claims appear to be an attempt to cover any medical use of a protein for which no viable medical uses have been shown by the applicant. Instead of specifying a method of treating a patient afflicted with a particular condition or specifying treatment to achieve a certain medical goal (such as amelioration of the condition), the claims set forth an ambiguity: administer to any patient in need of a substance a therapeutically effective amount of the substance. It remains unclear which patients need VEGF2, or when they need VEGF2, or how to determine how much VEGF2 they need.

6.8.4 For the same reason, the recitation in the claims of "a therapeutically effective amount" is vague and indefinite. One cannot ascertain a therapeutically effective amount when the therapeutic purpose and desired therapeutic outcome are unspecified.

6.9 As explained above (*e.g.*, in paragraphs 4.11-4.11.2.1), the opposed application does not describe a full length VEGF2, yet many claims might be said to encompass full-length VEGF2. With other claims, it is somewhat unclear exactly what the applicant intends to cover. For example, claim 1 recites "a VEGF2 polypeptide having the deduced amino acid sequence of Figure 1" and claim 29 contains a similar recitation. It is unclear whether this term is meant to limit the claims to a VEGF2 having only the amino acid sequence that is specifically recited and shown in Figure 1, or whether a VEGF2 having the sequence shown in Figure 1, plus additional VEGF2 sequence (or unrelated sequence) that was not taught in the opposed application, would also be encompassed.

6.10 Many claims (*e.g.*, claims 16-27, 34-50, and 57-61) try to delimit the invention with terms such as "a polypeptide which binds an antibody capable of binding to VEGF2." This terminology is ambiguous, because antibody-polypeptide interactions are not all-or-nothing interactions. Rather, such interactions are characterized by levels of specificity for a particular antigen, or by quantitative measurements of affinity, for example. There is no indication whether the claims are intended to encompass polypeptides that weakly cross-react with antibodies raised to VEGF2, or for that matter encompass situations where an antibody strongly binds to a different polypeptide (such as VEGF, or PDGF, or BR3P) and weakly cross-reacts with VEGF2.

6.11 Many claims in the opposed application use the term "isolated." This term would normally be clearly understood to reflect the separation of a particular item from amongst other items. However, the specification of the opposed application provides its own, somewhat broader definition: "The term 'isolated' means that the material is removed from its original environment (*e.g.*, the natural environment if it is naturally occurring). For example, a naturally-occurring polynucleotide or polypeptide present in a living animal is not isolated, but the same polynucleotide or DNA or polypeptide, separated from some or all of the coexisting materials in the natural system, is isolated. Such polynucleotide could be part of a vector and/or such polynucleotide or polypeptide could be part of a composition, and still be isolated in that such vector or composition is not part of its natural environment." (Specification at page 10, middle paragraph.) Thus, the definition of "isolated polynucleotide" or "isolated polypeptide" in the opposed application technically could embrace, for example, blood, serum, or tissue samples that are removed from a living organism, or cultured cell lines, which are separated from some or all of the coexisting materials in the natural system (the host organism). Likewise, the definition of "isolated" would appear to embrace an entire cDNA library that includes a VEGF2 cDNA in admixture with other cDNAs representing all other genes expressed in a cell or tissue. The VEGF2 cDNA in such a library is not "isolated" from the other cDNAs, but it is separated from some or all of the

coexisting materials in the natural system from which the library was derived. Thus, it is possible that the patent applicant intends "isolated" to have a broader meaning than scientists would ordinary attribute to the term.

Not a Manner of Manufacture

A. Introduction

7.1 As a result of my involvement in this matter it is my understanding that, under Australian Patent Law, a valid patent may not be granted for an alleged invention where the specification describes as the invention that which encompasses what is already known and referred to in the specification or where the specification merely describes an alleged invention in terms of a known and desired goal, without describing how that goal may be attained.

B. Analysis

7.2 In my opinion, the alleged invention as claimed in claims 1-5, 9-15, 19-28, 34-39, 46-48, 50-54, and 56-61, at least, of the opposed application was not the first disclosure of the subject matter of the opposed application. This is clear from the description provided in the specification itself. In addition to my discussion in the following sub-paragraphs I repeat by cross-reference my discussion in paragraph 2.7 and sub-paragraphs thereto.

7.3 In my opinion the claims of the opposed application include the polynucleotide sequence of VEGF2 and the encoded VEGF2 protein together with any biological activity of that protein. However, in describing a polynucleotide sequence which encodes a VEGF2 polypeptide, but without providing any demonstration of the biological activity of that encoded polypeptide, it is my opinion that the opposed application provides nothing more than a mere chemical curiosity.

7.3.1 The specification describes at page 5, lines 22 to 24, that the polynucleotide of the invention was "discovered" in a cDNA library derived from early stage human embryo week 9. The polynucleotide sequence was determined, and the encoded amino acid sequence was deduced and shown to have

homology to three known growth factor proteins (page 5, lines 24 to 30). The "highest homology" exhibited by the "protein" encoded by the polynucleotide of the alleged invention was 30% amino acid identity with VEGF. The specification states that the protein also exhibited homology to PDGFα (23%) and to PDGFβ (22%). On the basis of this homology the encoded polypeptide was speculated to have certain biological activity.

7.3.2 As at March 1994 (which I understand to be the alleged priority date of the opposed application), I would not have considered, and still to this day do not consider 22% to 30% amino acid identity between proteins to be soundly predictive of the biological activity of proteins either in a general sense or specifically in relation to growth factors or specifically in relation to the particular growth factors with which the opposed application is concerned. In my opinion, therefore, the degree of amino acid sequence identity between the subject sequence of the opposed application and the prior art growth factors is used merely for the purpose of unjustified speculation as to the nature of the biological activity of the polypeptide of the opposed application. The opposed application provides no evidence that convinces me that any polypeptide disclosed therein, much less any fragment, analogue, or derivative of that polypeptide, has the asserted biological activity. As further support of my opinion that the opposed application is directed to a mere chemical curiosity I incorporate by reference my discussion at paragraphs 2.3 and 4.6 and sub-paragraphs thereto.

7.4 Claims 1-5, 9-15, 19-28, 34-39, 46-48, 50-54, and 56-61, at least, are directed to an active fragment, analogue or derivative of VEGF2, and or to a polynucleotide encoding an active fragment, analogue or derivative of VEGF2. The opposed application speculates as to the nature of the biological activity of the VEGF2 polypeptide. However, there is no demonstration of VEGF2 biological activity in the specification and I have already stated that I believe the basis upon which the inventors speculate as to the nature of the biological activity is not sound.

Therefore, in so far as the claims of the opposed application are notionally limited by reference to biological activity or the requirement that the polypeptide be active I believe that they are directed merely to a desired goal.

7.4.1 This must be said to be the case even more so in respect of the claims directed to fragments, analogues, or derivatives of the disclosed sequence. In my opinion claims 1-5, 9-15, 19-28, 34-39, 46-48, 50-54, and 56-61 of the opposed application define an invention pertaining to fragments and/or analogues and/or derivatives of VEGF2 that possess VEGF2 activity, or the polynucleotides that encode such fragments, analogues or derivatives. However, the specification provides no demonstration or evidence of fragments, analogues or derivatives having VEGF2 activity as I explain in detail in paragraphs 4.6 to 4.8 and sub-paragraphs thereto.

7.5 Claims 51, 52 and 54 of the opposed application are directed to methods of treatment which utilise the polypeptide(s) or polynucleotide(s) of the opposed application. In addition to my discussion in paragraph 7.4 and sub-paragraphs thereto, I believe that these claims are directed to mere known and desired goals as illustrated by the fact that the specification contains no activity assay or activity demonstration (see paragraphs 2.3 and 4.6, and sub-paragraphs thereto, above).

7.6 The opposed application teaches that VEGF2 is a polypeptide shown in Figure 1 comprising 350 amino acid residues of which approximately the first 24 amino acids represent the leader sequence which is cleaved off to yield a mature VEGF2 of 326 amino acids (see, *e.g.*, specification at page 4, last 8 lines, and page 5, last paragraph). I refer to my discussion of paragraph 4.11 and sub-paragraphs thereto wherein I state that VEGF2 as described in the opposed application is known to be missing 69 amino acid residues at the beginning of the molecule. In my opinion this means that VEGF2 as taught in the opposed application lacks a true signal peptide and so would not be expressed and secreted by eukaryotic host cells in the manner alleged in the opposed application. The opposed application contains no evidence or successful expression and secretion from a cell, or even any attempt to

do so. Accordingly, as VEGF2 as taught in the opposed application is neither demonstrated to possess biological activity nor is likely, in my opinion, to be capable of expression and secretion from a host cell, it represents nothing more than a mere chemical curiosity as it is unlikely to be useful for expression and secretion without significant further development. I repeat by cross-reference my discussion of paragraphs 4.7 and 4.11, above, and sub-paragraphs thereto.

Summarizing Remarks

8.1 It may be helpful for me to distill the foregoing analysis into a few summarizing remarks.

8.2 In terms of its contribution to the public knowledge, the opposed application can, at best, be said to provide a previously undescribed sequence of nucleotides from the human genome. Beyond the new sequence, most of the opposed application appears to be "stock" text that the applicant, HGS, used in many recombinant DNA patent applications during the relevant time period, irrespective of the type of DNA (or encoded protein) that was being claimed.

8.3 There are several noteworthy details to the VEGF2 invention that are *absent* from the opposed application, *i.e.*, that were *not* provided to the public.

8.3.1 First and foremost, it is clear with the benefit of hindsight that the sequence provided in the opposed application in not even a complete VEGF2 sequence. The sequence provided is missing about 69 upstream codons, including the VEGF2 signal sequence.

8.3.2 In addition to providing a sequence that is incomplete, the opposed application has internal, unexplained inconsistencies between the partial VEGF2 sequences in its Figure, its Sequence Listing, and its biological deposit.

8.3.3 The opposed application fails to provide a VEGF2 activity assay or provide any evidence of a VEGF2 biological activity.

8.4 The patent applicant has sought extremely broad patent protection notwithstanding the limited nature of the disclosure to the public.

8.4.1 Notwithstanding the teaching of only a partial VEGF2 sequence, the applicant seeks patent protection using "comprising" claims that would encompass a full length VEGF2 sequence that the applicant considers to be an invention that is separately patentable in its own right.

8.4.2 Notwithstanding the teaching of only a partial VEGF2 sequence and the failure to teach a definitive VEGF2 biological activity or VEGF2 biological activity assay, the applicant seeks protection for "hybridizing" polynucleotides (and encoded polypeptides) and any polypeptides that bind antibodies that bind VEGF2 and that possess VEGF2 activity or inhibit VEGF2 activity. The relevant claims are so broad that they encompass prior art growth factor polynucleotides and polypeptides (or obvious variants thereof), and might be asserted to encompass growth factor polynucleotide and polypeptide discoveries of others that are separate and distinct from the partial VEGF2 taught in the opposed application.

8.4.3. Notwithstanding the failure to characterize VEGF2 biological activity or its functions in the human body, the applicants have claimed therapeutic regimens that involve administering VEGF2 to patients "in need of VEGF2" and administering VEGF2 inhibitors to patients "having need to inhibit VEGF2."

AND I MAKE this solemn declaration by virtue of the Statutory Declarations Act 1959, and subject to the penalties provided by that Act for the making of false statements in

statutory declarations, conscientiously believing the statements contained in this declaration to be true in every particular.

DECLARED at Melbourne

this 16th day of February 2000

P. Rogers

Peter Adrian Walton Rogers

BEFORE ME:

Elizabeth Kennedy

ELIZABETH KENNEDY
B.A. LL.B (Hons) LL.M (Melb) SOLICITOR
SOUTHERN HEALTH CARE NETWORK
DAVID ST. DANDENONG
A natural person who is a current practitioner
within the meaning of the Legal Practice Act 1996

AUSTRALIA

Patents Act 1990

IN THE MATTER OF Australian Patent Application Serial No 696764 by Human Genome Sciences, Inc.

-and-

IN THE MATTER OF Opposition thereto by Ludwig Institute for Cancer Research

THIS IS Exhibit 1 referred to in the Statutory Declaration of Peter Adrian Walton Rogers made before me this 16th Day of February, 2000

Elizabeth Kennedy

ELIZABETH KENNEDY
B.A. LL.B (Hons) LL.M (Melb) SOLICITOR
SOUTHERN HEALTH CARE NETWORK
DAVID ST. DANDENONG
A natural person who is a current practitioner within the meaning of the Legal Practice Act 1996.

CURRICULUM VITAE

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DATE OF BIRTH: 1st September, 1955.

PLACE OF BIRTH: London, England.

MARITAL STATUS: Wife Cheryl and two children,
Elizabeth 13 and Gillian 11

CITIZENSHIP: Australian and British
(Dual Nationality)

QUALIFICATIONS: 1977 BSc (Hons)
1983 PhD

INDEX PAGE

1. EDUCATION

1966 - 1973
Abingdon School, Berkshire, UK
9 O-Levels, 3 A-levels.

September 1974 - June 1977
Liverpool University, U.K. B.Sc. Honours (IIA) in Marine Biology. Title of thesis: A Histological Study of Wound Healing in Plaice (Pleuronectes platessa).

2. POSTGRADUATE TRAINING

February 1980 - December 1982
Ph.D. studies, Flinders University, South Australia. Title of thesis: Rat Uterine Microvasculature During the Oestrous Cycle and Early Pregnancy.

March - June 1994
Mini sabbatical leave to work with Professor Steve Smith and Dr Stephen Charnock-Jones in the Department of Obstetrics and Gynaecology at Cambridge University. Studies included development of methods for non-isotopic techniques of in situ hybridisation and an investigation of VEGF expression in endometrium from women with progestin-induced breakthrough bleeding.

March-July 1988
Mini sabbatical leave to work with Prof. Gary Hodgen and Dr Ted Anderson at the Jones Institute Research Laboratories, Eastern Virginia Medical School, Norfolk, Virginia, USA. Studies included the development of a new technique for the isolation and long-term culture of human endometrial endothelial cells.

3. PREVIOUS RESEARCH POSITIONS

1993 -1995
NH&MRC Senior Research Fellow (levels 4-6), Dept. Obstetrics & Gynaecology, Monash University.

July 1986 - December 1992
Senior Research Fellow Grade 1. Dept. Obstetrics & Gynaecology, Monash University.

1985-1987
Worked on an intermittent basis as a scientific consultant for the company IVF Australia. Duties included advising on the establishment of IVF clinics in the United States, laboratory design and staff recruitment and training. During this period, numerous trips to the United States were made to provide training, technology transfer and assist in the process of opening new IVF clinics.

April 1985 - July 1987
Scientific Director of the Monash IVF Programme.

March 1985 - June 1986
Research Fellow Grade II, Dept. Obstetrics & Gynaecology, Monash University.

March 1983 - March 1985
Research Fellow Grade I, Department of Obstetrics & Gynaecology, Monash University.

December 1977 - December 1979
Research assistant to Dr. B.J. Gannon, Department of Human Morphology, School of Medicine, Flinders University, South Australia.

4. PRESENT APPOINTMENT

1996 to present: NH&MRC Principal Research Fellow, Dept. Obstetrics & Gynaecology, Monash University
1998 to present: Associate Professor, Dept. Obstetrics & Gynaecology, Monash University

5. COLLABORATIONS

As part of my work with the World Health Organisation Task Force on Long-Acting Systemic Agents for Fertility Regulation I am involved in several collaborative research projects with staff in the Human Reproduction Study Group at the University of Indonesia. The staff that I have the most involvement with are Dr Biran Affandi, Dr Sri Bekti Subakir, Dr Sugito Wonodirekso and Dr Julianto Witjaksono. This work investigates various aspects of endometrial breakthrough bleeding caused by long-term progestin contraception. This collaboration has been funded continuously by the World Health Organisation from 1990 with funds currently committed until the year 2000. I visit Jakarta 2-3 times per year where I am also involved in research training and technology transfer.

I collaborate with a number of people on different components of my research programme, including:
Dr Peter Dockery, University of Cork, Ireland; Morphometric studies on endometrial vasculature.
Dr Hillary Critchley, Edinburgh, UK. Menorrhagia studies.
Dr Judy Abraham, Scios Corporation, USA. Supply and testing of VEGF121.
Prof. Sangkot Marzuki, Director, Eijkman Institute, Jakarta. Pre-eclampsia studies.
Dr Chris Murphy, Dept. Anatomy & Histology, University of Sydney, Endometrial ultrastructure.
Dr Steve Stacker, Dr Marc Achen, Ludwig Institute, Melbourne. Various studies on VEGF
Dr Victor Lee, Kryocor Pty. Ltd., North Melbourne. Growth of endothelial cells on vascular grafts.
Dr Lois Salamonsen, Prince Henry's Institute, Melbourne. Norplant effects on the endometrium.
Prof. John Leeton, Monash IVF. Preparation of recipient endometrium for implantation
Dr Beatrice Susil, Anatomical Pathology, Monash Medical Centre. Endometrial and ovarian pathology.
Dr Euan Wallace, Dept. Obstetrics & Gynaecology, Monash University. Pre-eclampsia studies.
Dr Beverley Vollenhoven, Dept. Obstetrics & Gynaecology, Monash University. Fibroid studies.

I have also provided anti-VEGF antisera that I produced to Dr Tailoi Chan at Sydney University and Dr Wayne Tilley at Flinders University.

6. EVIDENCE OF NATIONAL AND INTERNATIONAL PROFILE

In 1998 I was 1 of only 2 Australian scientists invited to join the inaugural Editorial Board of the new international journal "Angiogenesis"

In recognition of the work performed by my group at Monash, the World Health Organisation, in conjunction with NIH from the US, will be held an international symposium on progestin contraceptives and endometrial breakthrough bleeding at Monash Medical Centre on May 4-5, 1999. This meeting was attended by approximately 15 international speakers comprising most of the leading research workers in the field. I was chairman of the organising committee for this meeting.

I have been invited to contribute chapters or reviews to several recent international books, including:
ROGERS PAW (1999) Menstruation. In: Estrogens and progestogens in clinical practice. Eds. I. Fraser, R. Jansen, R. Lobo and M. Whitehead. Churchill Livingstone, Edinburgh. U.K.
ROGERS PAW, LEETON J (1999) Uterine receptivity and embryo transfer. In: Handbook of In Vitro Fertilization 2nd edition. Gardner D, Trounson AO, Eds.
ROGERS PAW (1997) The endometrial vascular bed. In: Clinical Disorders of the Endometrium and Menstrual Cycle. Eds. I. Cameron, I. Fraser, S. Smith. Oxford University Press, New York pp 31-45.
I am also one of 4 international editors for a proposed book on vascular morphogenesis in the female reproductive system which has been accepted for inclusion by Springer Verlag in the Cardiovascular Molecular Morphogenesis Series.

In September 1994 I conducted a review on behalf of WHO and the Indonesian Government Department of Family Planning (BKKBN) on the research activities of Human Reproduction Study Groups at Universities in Jakarta, Surubaya and Medan.

Invitations To Speak Overseas And At International Meetings
4th World Congress on In Vitro Fertilization, Melbourne, November 19-22nd, 1985. Plenary Lecture.

World Health Organisation seminar on endometrial bleeding and contraceptive use, Jakarta, Indonesia, November 17-18, 1989. Invited speaker.

United States - Australia Cooperative Workshop, "Successful maternal recognition of pregnancy: Signalling between the conceptus and maternal system." Sponsored by The National Science Foundation, USA, and The Department of Industry Commerce and Development, Australia. University of Hawaii, Honolulu, July 1-3rd, 1991. 2 invited papers.

National Institute of Child Health and Human Development, USA; Symposium on "Exogenous hormones and dysfunctional bleeding." NIH, Bethesda, Maryland, USA. May 4-6th, 1992. Invited speaker.

VIIIth World Congress on Human Reproduction, Bali, Indonesia. April 4-9th. 1993. Basic

studies on endometrial bleeding in norplant users.

14th Asian and Oceanic Congress of Obstetrics and Gynaecology, Manila, November 14-19th, 1993. Research on progestogen-induced vaginal bleeding: a collaboration between Indonesia and Australia.

31st May 1994; Department of Obstetrics and Gynaecology at Edinburgh University, "Vascular growth in normal and Norplant treated endometrium".

3rd June 1994; Department of Obstetrics and Gynaecology, Queens University of Belfast, "Angiogenesis in endometrial bleeding disorders".

First International Meeting of World Placenta Associations, October 24-28, 1994. Sydney. Invited plenary lecture: Current studies on human implantation.

Eighth Symposium of the Australian and New Zealand Microcirculation Society. Auckland, Feb. 3-5, 1995. Invited lecture: Reproductive angiogenesis.

Second International Symposium on IVF, Seoul, Korea, April 29-30, 1995. Invited lecture, "Maternal age effects on the endometrium."

World Health Organisation sponsored meeting in Bali, October 14-15th, 1995. "Current research on progestin-only contraceptives and endometrial bleeding".
International Ferring Symposium on Function and Dysfunction of the Non-Pregnant Uterus. A Satellite Symposium to the 1997 ESHRE Annual Meeting. Germany, June 19-21, 1997. Title: Endometrial microvascular growth in normal and dysfunctional states".

Group seminar at the Department of Surgery, Harvard University, Boston, USA. 14 August 1997. Title: "Angiogenesis in reproductive tissues".

WHO/NIH Symposium on Steroids and Endometrial Breakthrough Bleeding, May 4-5, 1999. Title:- Growth and regression of the endometrial vasculature.

Gordon Research Conference on Angiogenesis and Microcirculation, Rhode Island, USA. Chairman and Discussion Leader on Angiogenesis in Reproduction session.

Invitations To Speak In Australia And At National Meetings

Australian Society for Reproductive Biology. Embryo Transfer Satellite Symposium, Adelaide, 25th August 1985. Invited speaker.

Australian and New Zealand Microcirculation Society, Fifth Symposium, Canberra, 10-12th February, 1989. Invited Speaker.

Fertility Society of Australia, 1989 Annual Scientific Meeting. Satellite symposium on embryology. Invited speaker.

Fertility Society of Australia, 10th Annual Conference, Lorne, Victoria. November 18-22nd,

1991. Invited speaker

Serono Symposium on Oocyte Donation, Melbourne, November 22-24th, 1991. Plenary lecture.

Australian Menopause Society, 3rd Congress, Melbourne, April 5-8th, 1992. Basic mechanisms of endometrial bleeding.

2nd Baker Institute Symposium, Melbourne, 11-13th December, 1992. Endometrial angiogenesis.

Howard Florey Institute of Experimental Physiology and Medicine. Seminar on "Endometrial angiogenesis - Basic and clinical studies". Melbourne, October 14th 1993.

Fertility Society of Australia, Embryo-Uterine Coculture Workshop, November 6 1993, Sydney. Invited lecture, "Animal Models for Implantation".

Monash Medical Centre Grand Round. August 2 1994. Angiogenesis in reproductive tissues.

International Symposium on Contemporary Microsurgery - Clinical and Research Vistas, Melbourne, St Vincents/Bernard O'Brien Institute. February 13-14th 1996. Title "The physiological basis of the angiogenic process".

Ludwig Institute 1996 Seminar Program. 21st June 1996. Title "Angiogenesis in the Female Reproductive Tract".

Medical Research Week, 4th June 1997. Title "Endometriosis".

Victorian Obstetrics and Gynaecologists Specialists seminar, July 24 1997. Title: "Basic studies on endometriosis".

CRC on Vertebrate Biocontrol Centre. Canberra May 14, 1998. Title: "Angiogenesis and implantation in the rat".

St Vincent's Institute of Medical Research 9th June 1998. Title: "Angiogenesis in the female reproductive tract"

PHIMR Symposium 15-16 October, 1998, Symposium on Title: Endometriosis. Why and How?

Australian and New Zealand Microcirculation Society, Tenth Symposium, Adelaide, 28-29 January, 1999. Invited Speaker.

The University of Melbourne, Department of Pharmacology, 26 April 1999. Title: "Angiogenesis in reproductive tissues".

Institute of Reproduction and Development Symposium, 7-8 May 1999. Title:-"Angiogenesis

in ovarian cancer".

Monash University Department of Anatomy Seminar Series, August 4, 1999. Title:- Angiogenesis in reproductive tissues".

Awards

Australian Society for Fish Biology. Gilbert P. Whitley Memorial Award for best scientific presentation by a student. 1980 Annual Meeting.

Fertility Society of Australia, 5th Annual Scientific Meeting, Adelaide, December 1986. Serono-CSL award for best scientific presentation.

Fertility Society of Australia, 6th Annual Scientific Meeting, Sydney, November 1987. Merrell-Dow award for best poster presentation.

Australian and New Zealand Microcirculation Society. Best paper by a young scientist at 1989 meeting.

Awards Received By Group Members

Keren Abberton, PhD student. Australian and New Zealand Microcirculation Society. Best paper by a student at 1997 meeting

Maxine Orre, PhD student. Second Peter Mac Symposium. New Strategies for Cancer Detection and Therapy. Best poster award, 1997

Caroline Gargett, Postdoc. Tenth Australian and New Zealand Microcirculation Symposium. Best talk by a young scientist, 1999

7. POSTGRADUATE AND UNDERGRADUATE TEACHING

Completed Theses

PhD

1991-1994; Anne Macpherson. Title of Thesis: Endometrial angiogenesis

1994-1998; Maxine Orre. Title of Thesis: Angiogenesis in tumours of the ovary and breast

MD

1991-1993; Dr. Neil McClure. Title of Thesis: Aspects of ovarian angiogenesis and the ovarian hyperstimulation syndrome

1992-1994; Dr Mary Wingfield. Title of Thesis: Endometrial angiogenesis and CA125 in women with endometriosis

M. Reprod. Sci.

1990; Keren Abberton. Title of Thesis: A signal for vascular endothelial cell migration in rat and human endometrium

1996-1997; Linda Hii. Title of Thesis: Endometrial expression of integrin v3: Relationship to angiogenesis and uterine receptivity for implantation

B.Med Sci
1992; David Archbold. Title of Thesis: The expression of LCA, LFA-1and MAC-1 within human endometrium throughout the menstrual cycle
1998; Robert Casey. Title of Thesis: Microvascular structure and function in human fibroids.

BSc Honours
1993; Fiona Kelly. Title of Thesis: Microvascular heterogeneity of normal human endometrium
1993; Fiona Lederman. Title of Thesis: Endometrial angiogenesis: production of endothelial cell migratory factor in vitro
1994; Jason Palmer. Title of Thesis: Vascular basement membrane composition in the endometrium of women receiving long-term progestin contraception
1996; Mozhgan Lotfi-Miri. Title of Thesis: Ovarian angiogenesis in the rat.

Postgraduate Students: Under Supervision Or Writing Up
PhD
1995-present; Keren Abberton. Topic of Thesis: Development and function of endometrial arterioles (Submission due April 1999)
1997-present; Dr Anne Rosamilia. Topic of Thesis: Cellular and vascular aspects of interstitial cystitis.
1997-present; Mozhgan Lotfi-Miri. Topic of Thesis: Regulation of endometrial angiogenesis during early pregnancy in the rat (Candidate currently on 12 months maternity leave)
1999-present; Bambang Heryanto. Topic of Thesis: Mechanisms of endometrial angiogenesis

M.Reprod. Sci
1998-1999; Corey Heffernan. Topic of Thesis: Angiogenesis inhibitors in human endometrium (Submission due July 1999)

BSc Honours
1999; Marina Zaitseva. Topic of Thesis: Regulation of vascular endothelial growth factor receptors in human myometrial microvascular endothelial cells

Undergraduate Teaching Experience
At Monash University I give a limited number of lectures to students in the Diploma and Masters of Reproductive Science courses, as well as providing supervision for various assignments and a practical class on immunohistochemistry. In the past I have given occasional lectures to the 5th year medical students, as well as to physiology, anatomy and veterinary students. At Flinders University from 1978-1982 I was heavily involved in running first year biology practical classes, as well as demonstrating anatomy and histology to medical students.

8. ADMINISTRATIVE RESPONSIBILITIES

Community Service: Trustee for the Jean Hailes Menopause Foundation (1988 to present)
In 1988 I became involved with 5 other people in establishing the Jean Hailes Foundation in honour of the life work of Dr Jean Hailes who died in November of that year. The Jean Hailes Foundation is a non-profit organisation specialising in the management of women's health. The Trust under which the Foundation operates, specifies 3 major activities:- clinical services,

research, and education, with the latter having a strong focus on health promotion and illness prevention. Since the opening of the Clinic in 1992, the Foundation and its activities have grown at a dramatic rate. In the financial year 1997-1998, the Foundation had a turnover in excess of $1.7million. As one of five Trustees, I take responsibility for a range of policy and financial issues within the organisation. I have represented the Jean Hailes Foundation in discussions with both State and Federal Health Ministers and the work of the Foundation enjoys strong recognition from both these levels of government. Among the many activities currently on the agenda at the Foundation is the establishment of the Jean Hailes Chair in Women's Health to be established in the Monash University Department of Obstetrics and Gynaecology with funds raised by the Jean Hailes Foundation.

Committee Memberships And Management Contributions

1999 to present	Faculty of Medicine Research Strategic Planning Committee (Sub-committee of the Faculty of Medicine Research Committee)
1996 to present	Chairman, Department of Obstetrics and Gynaecology postgraduate students committee
1995 to present	Department of Obstetrics and Gynaecology Executive and Finance Committee
1992 to present	Company Director for Menoserve Pty Ltd, trading entity for the Jean Hailes Menopause Foundation.
1989 to present	Trustee and Foundation Board member of The Jean Hailes Menopause Foundation Trust.
1988 to present	Scientific Director, Monash IVF Donor oocyte program.
1988 to present	Department of Obstetrics and Gynaecology monthly Academics meetings.
1996 - 1998	Chairman, Monash Medical Centre Animal Experimentation Ethics Committee
1987 - 1998	Member, Monash Medical Centre Animal Ethics Committee
1997	Member, Monash University Animal Welfare Committee
1995 - 1997	Member, Faculty of Medicine B. Med. Sci. Committee
1993 - 1997	Member, Institute of Reproduction and Development Executive.
1993 - 1997	Department of Obstetrics and Gynaecology representative on Monash University Faculty of Medicine Board.
1989 - 1997	Board Member, Monash University Centre for Reproductive Biology

1986 - 1988	Member, Queen Victoria and Monash Medical Centre Animal House Co-ordinating Committee
1987 - 1988	Member, Monash Medical Centre IVF Unit Executive
1985 - 1987	Monash University-IVFA Operations Committee
1984 - 1987	Member of Monash IVF Executive
1984 - 1987	Member of Monash IVF Finance Committee
1985 - 1986	Chairman, Obstetrics & Gynaecology Animal Ethics Committee
1984 - 1985	Obstetrics & Gynaecology Representative on University Biomedical Library Committee
1981 - 1982	Postgraduate Representative on Flinders Medical Centre School Board
1981 - 1982	Member, Flinders Medical Centre Audio Visual Advisory Committee
1982	President, Flinders University Sports Association
1980 - 1982	President, Flinders University Underwater Club
1983 - 1986	National Testing Officer, Cave Diving Association of Australia

9. PEER REVIEW AND SCIENTIFIC DISCIPLINE INVOLVEMENT

Refereeing For International Journals And Granting Bodies

I am on the editorial board of the new international journal, Angiogenesis, and have served on the Editorial Board for the Chinese Journal of Physiology. I have acted as an ad hoc referee for a number of scientific journals, including: Journal of Reproduction and Fertility, Biology of Reproduction, Fertility and Sterility, Human Reproduction, Human Reproduction Update, Molecular Human Reproduction, Reproduction Fertility and Development, Journal of Endocrinology and International Journal of Cancer.

I referee grant applications for numerous agencies including National Health and Medical Research Council, Australian Research Council, various Australian Anti Cancer agencies, the Wellcome Foundation, the Health Research Council of New Zealand and the Biotechnology and Biological Sciences Research Council. In February 1999 I was a scientific grant referee for Indonesian Ministry of Education and Culture, Directorate General of Higher Education

Society Memberships

Australian Society for Reproductive Biology
Australian Society for Medical Research
Australian Fertility Society (Foundation member)
Australian & New Zealand Microcirculation Society (Foundation member and President 1997-1998)
American Society for Reproductive Medicine (Formerly The American Fertility Society)
Society for the Study of Reproduction (USA)

Scientific Committee Memberships And Society Offices Held

1998 - 1999	Chairman, Organising committee for WHO/NIH symposium on contraceptives and endometrial bleeding to be held at Monash Medical Centre May 4-5, 1999
1998 - 1999	Chairman, Organising Committee for Institute of Reproduction and Development annual symposium. "Angiogenesis in Reproductive Tissues" to be held at Monash Medical Centre May 7-8, 1999.
1997 – 1998	President, Australia and New Zealand Microcirculation Society
1996 - 1997	Chairman of organising committee for 1997 Australian and New Zealand Microcirculation Society Conference in Melbourne, January 30 - February 1, 1997.
1994	Member of organising committee, Carl Wood Festschrift, "Reproductive medicine beyond 2000".
1994	Convenor, Scientific Program Organising Committee, Australian Society for Medical Research 33rd National Scientific Conference, Melbourne, 27-30 November 1994

1992	Convenor, Victorian ASMR Medical Research Week.
1991	Lecture program organiser, Victorian ASMR Medical Research Week.
1990-1991	Organising committee and session chairman, Australian and New Zealand Microcirculation Society 1991 Scientific Meeting.
1989	Organiser and Chairman, Fertility Society of Australia Embryology Symposium
1985	Organizing Committee, 4th World Congress on IVF, Melbourne, Australia

10. RESEARCH GRANT SUPPORT

I continue to run a group of between 10 and 15 staff and students with 80% of funding being obtained from peer review national and international sources. Over the 5 years, 1994-1998 I attracted approximately $1.6 million in outside research funds, and my research group published 46 peer review publications, 14 chapters or invited reviews, and 53 conference abstracts.

Research Grants And Funding To Dr. P.A.W. Rogers

1985	Special research grant, Monash University. The role of the uterine microvasculature in early implantation	$7,500
1985	Special grant from Serono and Commonwealth Serum Laboratories towards the establishment of a departmental histology laboratory	$28,000
1985	Special grant of equipment towards the development of a high purity water system for IVF application from Millipore Australia	$20,000
1985	Special grant from Organon towards a technical assistant's salary	$10,000
1985	Donation from IVF patient towards microscope equipment for histology laboratory	$6,000
1986-1988	NH&MRC. In vivo and ultrastructural studies on implantation and uterine receptivity	$116,285
1986	William Buckland Foundation. Histological investigation of the anterior eye chamber embryo implantation model	$3,060
1986	Special Research Grant, Monash University. Ultrastructural studies of human endometrium relating to uterine receptivity for implantation	$5,000

1987	NH&MRC. Application for an electron microscope for studies in reproduction. Chief Investigator: Dr. A. Trounson, Senior Investigators: Drs. P. Rogers, A. Walker, H. Sathananthan	$87,000
1987	Clive and Vera Ramaciotti Foundation. Shared equipment for measuring red blood cell velocity from videotape records of intravital blood flow in the micro-circulation. (Other Chief Investigators: Prof. B. Gannon, Prof. P. O'Brien)	$10,000
1987	William Cook Australia Pty. Ltd. Technical salary support	$5,000
1987	R.A. Hallenstein Charitable Trust. The role of uterine factors in human infertility	$1,000
1988	Brockhoff Foundation. Ultrastructural studies on human post-menopausal endometrium following steroid replacement therapy	$26,144
1988	R.A. Hallenstein Charitable Trust	$3,000
1989-1991	NH&MRC. Molecular changes in the plasma membrane of human uterine epithelial cells	$90,150
1989	CONRAD. Isolation and culture of human endometrial endothelial cells	$18,797
1989	R. A. Hallenstein Charitable Trust	$3,000
1989	Monash Research Fund. Endometrial response to different postmenopausal hormone replacement therapies	$2,550
1990	Monash Medical Centre. Endometrial microvascular response to oestrogen	$3,000
1990	Sunshine Foundation. Endometrial microvascular response to oestrogen	$5,000
1990	Perpetual Executors and Trustees. Endometrial microvascular response to oestrogen	$5,000
1990	Helen Schutt Foundation. Endometrial vascular response to oestrogen	$5,000
1990	Infertility Medical Centre. Correlation of endometrial histology, morphometry and ultrasound appearance with superovulation protocol for IVF	$12,000
1990-1993	World Health Organisation. The aetiology of increased endometrial bleeding in Norplant users; the role of local factors	$300,000

1990	Buckland Foundation. Endometrial vascular response to oestrogen	$5,000
1990	R. A. Hallenstein Charitable Trust. Endometrial vascular response to oestrogen	$3,000
1990	Collier Charitable Fund. Equipment grant to purchase a microhysteroscope for O&G Dept	$2,500
1991-1993	NH&MRC. A study of endometrial microvascular function during embryo implantation	$219,663
1991-1993	NH&MRC. The role of local endometrial factors in perimenopausal uterine bleeding	$190,937
1991	Helen M. Schutt Trust. Equipment grant to purchase a microhysteroscope for O&G Dept	$3,000
1991	William Angliss Charitable Fund. Equipment grant to purchase a microhysteroscope for O&G Dept	$2,000
1992	Collier Charitable Fund. Purchase of 2 chemotaxis chambers	$2,250
1992	Sunshine Foundation, Equipment grant to purchase a set of objective lenses for a new microscope	$4,828
1993-1997	NH&MRC. Local regulation of endometrial angiogenesis (Senior Research Fellowship)	$211,745
1993-1995	NH&MRC. Local mechanisms influencing endometrial function in menorrhagia	$189,753
1993	Collier Charitable Trust. Purchase of image scanner	$2,750
1993	ANZ Trustees. Purchase of Zeiss microscope	$10,000
1993	ANZ Trustees. Menstrual disorders, Impact on womens health	$10,000
1994-1996	World Health Organisation. Local control of the endometrial vasculature in women receiving long-term progestogen contraception	$254,000
1994-1995	Anti-Cancer Council of Victoria. Role of vascular endothelial growthfactor in ovarian tumour angiogenesis	$64,000
1994-1995	Slezak Trust (Through The Jean Hailes Menopause Foundation). Control of vascular growth in ovarian cancer	$102,000

1994	The Arthur Wilson Memorial Scholarship in Obstetrics & Gynaecology. Spiral arteriole development in menorrhagia (Awarded to Dr Jacoba Kooy, postdoc in group)	$20,000
1994	British Council Travel Grant. Travel funds for UK sabbatical	$2,299
1994	Wellcome-Ramaciotti Research Travel Grant.	$1,500
1994	William Buckland. The mechanism of action of Danazol in the regression of human endometrium and microvascular density. (Awarded to Dr. Tseng Lau, postdoc in group).	$12,750
1995-1997	NH&MRC. Uterine microvascular-embryo interactions during implantation in the rat	$163,818
1996-1998	The Jean Hailes Menopause Foundation. Research support grant.	$15,000
1997	The Royal Australian College of Obstetrics & Gynaecologists. Arthur Wilson Memorial Scholarship in Obstetrics & Gynaecology.	$20.000
1996-2000	NH&MRC. Endometrial angiogenesis (Principal Research Fellowship Grant)	$958,883
1998-2000	World Health Organisation. Investigation of local mechanisms associated with progestin induced endometrial bleeding	$252,392
1998	Appel Family Bequest. Factors influencing fibroid growth and Development.	$12,500
1998	Contract Research with Kryocor Pty Ltd. Funds to establish endothelial Cell laboratory	$42,000

11. BRIEF OUTLINE OF PREVIOUS, CURRENT AND PROPOSED RESEARCH EXPERIENCE

1977-1979

Work as Research Assistant in laboratory of Dr B Gannon, Dept. Human Morphology, Flinders University. Projects included histology, ultrastructure, morphometry and vascular corrosion casting studies on the microvasculature of the mammalian small intestine, lungfish gills and tuna gills.

1980-1983

PhD studies on rat uterine microvascular structure and function. Techniques included ultrastructure, vascular corrosion casting, morphometry and in vivo microscopy.

1983-1985

Postdoctoral appointment with Monash IVF. During this period I gained expertise in all aspects of human IVF, including embryology, andrology, endocrinology, ovulation induction and cryopreservation. In addition, I obtained independent research funding for staff and equipment to establish my own basic endometrial/implantation research group.

1985-1987
Scientific Director, Monash IVF. Duties included overseeing and co-ordinating the scientific research projects associated with the Monash IVF programme, running the embryology laboratory, maintaining quality control and ensuring an adequate pregnancy rate, recruiting, training and supervising embryology staff (the IVF programme employed 6 embryologists at this time), preparing and participating in public information seminars and debates, and preparing submissions for government committees reviewing the legislation controlling and the funding for IVF in Australia. During this period I also ran my own basic research group studying endometrial function and implantation, and in 1986 obtained project funding from NH&MRC for studies on embryo implantation.

1988-1992
My primary activities during this period were obtaining funding for, and running, a number of basic research projects relating to menstruation, the pathology of abnormal uterine bleeding, embryo implantation, endometrial structure and function and the endometrial microvasculature. Specific research projects included; work on endometrial microvascular function in women using long-term progestin contraceptive implants, factors that cause increased endometrial bleeding in peri-menopausal women, and the response of the rodent endometrial microvasculature to the implanting embryo.

1993-1996
Major research interests included endometrial physiology, microvascular function, angiogenesis, and embryo implantation as well as a number of relevant gynaecological disorders including menorrhagia, endometriosis, peri-menopausal problems and contraceptive induced break-through bleeding. Developed considerable expertise in immunohistochemistry methodology.

1997- to present
My research interests continued to develop within the broad field of reproductive biology and angiogenesis. Specific interests include understanding of the mechanisms and regulation of physiological angiogenesis in reproductive tissues during the menstrual cycle, and alterations in the angiogenic process that occur in tumour tissues. A number of collaborations with clinical investigators within and associated with the Department of Obstetrics and Gynaecology include work on topics such as leiomyoma, interstitial cystitis, endometriosis, menorrhagia, and pre-eclampsia. More recently I have established an endothelial cell laboratory in conjunction with an industry partner with various projects investigating macro and micro vascular endothelial cell biology.

The Future
I will continue to develop the expertise within my group and the Obstetrics & Gynaecology Department to pursue basic studies in areas such as angiogenesis, endothelial cell biology, and microvascular function. More clinically oriented studies will continue into diseases such as

reproductive cancers, menorrhagia, endometriosis, leiomyoma, interstitial cystitis, and pre-eclampsia. We have developed significant expertise in techniques such as immunohistochemistry, image analysis and tissue culture (including isolation and culture of microvascular endothelial cells, and a range of primary cell separation and culture techniques). Another major strength is our ability to liaise with a large number of clinical staff both in Melbourne and overseas. This gives us rapid access to large collections of well characterised clinical material for our research studies. We also have capabilities in a range of other methodologies, including in situ hybridisation, PCR, Northerns, RPA and various biochemical techniques. The development and increasing contribution of Dr Caroline Gargett as a postdoc within the group is seen as a significant plus for the future. Similarly, the recent addition of Dr Euan Wallace as a specialist obstetrician and researcher to the Department has opened up major new opportunities for collaboration. At the present time these are being pursued in the form of a major research proposal on pre-eclampsia.

REFEREED PUBLICATIONS

1. GANNON BJ, ROGERS PAW, O'BRIEN PE (1980). Two capillary plexuses in human intestinal villi. Micron 11:447-448.

2. GANNON BJ, GORE RW, ROGERS PAW (1981). Is there an anatomical basis for a vascular counter current mechanism in rabbit and human intestinal villi? Biomed Res 2 suppl. 235-241.

3. SMITH MJ, ROGERS PAW (1981). Skulls of Bettongio lesueur (Mammalia: Macropodidae) from a cave in the Flinders Ranges, South Australia. Trans Roy Soc Sth Aust 105:217.

4. ROGERS PAW, GANNON BJ (1981). The vascular and microvascular anatomy of rat uterus during the oestrous cycle. Aust J Exp Biol Med Sci 59:667-679.

5. ROGERS PAW, MURPHY CR, GANNON BJ (1982). Changes in the spatial organization of the uterine vasculature during implantation in the rat. J Reprod Fert 65:211-214.

6. ROGERS PAW, MURPHY CR, GANNON BJ (1982). Absence of capillaries in the endometrium surrounding the implanting rat blastocyst. Micron 13:373-374.

7. ROGERS PAW (1982). The vascular and microvascular anatomy of the gill of the southern rock lobster Jasus novaehollandiae. Aust J Mar Freshw Res 33:1017-1028.

8. ROGERS PAW, MURPHY CR, ROGERS AW, GANNON BJ (1983). Capillary patency and permeability in the endometrium surrounding the implanting rat blastocyst. Int J Microcirc : Clin Exp 2:241-249.

9. ROGERS PAW, GANNON BJ (1983). The microvascular cast as a 3-dimensional tissue skeleton. Visualization of rapid morphological changes in tissues of the rat uterus. J Microsc 131:241-247.

10. ROGERS PAW, MURPHY CR, SQUIRES KR, MacLENNAN AH (1983). The effects of relaxin on the intra-uterine distribution and antimesometrial positioning and orientation of rat blastocysts before implantation. J Reprod Fert 68:341-435.

11. ROGERS PAW (1983). Rat uterine microvasculature during the oestrous cycle and early pregnancy. Ph.D. Thesis. Flinders University of South Australia, Bedford Park, South Australia.

12. GANNON BJ, BROWNING J, O'BRIEN P, ROGERS, PAW (1984). Mucosal microvascular architecture of the fundus and body of human stomach. Gastroenterology 86:866-875.

13. ROGERS PAW (1984). In vitro fertilization : a review. Aust J Med Lab Sci 5:5-13.

14. ROGERS PAW, TROUNSON AO (1984). In vitro fertilization: current state of the art. International Medicine 4:2-5.

15. WOOD C, DOWNING B, TROUNSON A, ROGERS P (1984). Clinical implications of developments associated with the technique of in vitro fertilization. Brit Med J 289:978-980.

16. TROUNSON A, ROGERS PAW, LUTJEN PJ, SATHANANTHAN H, HOPPEN H-O, YATES C, DE KRETSER D, LEETON J, HEALY D, WOOD C (1985). Human in vitro fertilization and embryo transfer. Acta Obstet Gynaec Jpn 37:1231-1240.

17. ROGERS PAW, MILNE BJ, TROUNSON AO (1986). A model to show uterine receptivity and embryo viability following ovarian stimulation for in vitro fertilization. J Vitro Fert Embryo Transfer 3:93-98.

18. TROUNSON A, HOWLETT D, ROGERS P, HOPPEN H-O (1986). The effect of progesterone supplementation around the time of oocyte recovery in patients superovulated for in vitro fertilization. Fertil Steril 45:532-535.

19. KOVACS GT, ROGERS P, LEETON J, TROUNSON AO, WOOD C, BAKER HWG (1986). In vitro fertilization and embryo transfer - prospects of pregnancy by life table analysis. Med J Aust 144:682-683.

20. ROGERS P, MOLLOY D, HEALY D, McBAIN J, HOWLETT D, BOURNE H, THOMAS A, WOOD C, JOHNSTON I, TROUNSON A (1986). Cross-over trial of superovulation protocols from two major in vitro fertilization (IVF) centres. Fertil Steril 46:424-431.

21. OKAMOTO S, HEALY DL, HOWLETT DT, ROGERS PAW, LEETON JF, TROUNSON AO, WOOD EC (1986). An analysis of plasma estradiol concentrations during clomiphene citrate - human menopausal gonadotropin stimulation in an in vitro fertilization-embryo transfer program. J Clin Endocrinol Metab 63:736-740.

22. KOVACS GT, SHEKLETON P, LEETON J, ROGERS P, WOOD C, BUTTERY B, RENOU P, DAVIDSON G (1987). Ectopic tubal pregnancy following in vitro fertilization and embryo transfer under ultrasonic control. J Vitro Fert Embryo Transfer 4:124-126.

23. LENZ S, LEETON J, ROGERS P, TROUNSON A (1987). Transfundal transfer of embryos using ultrasound. J Vitro Fert Embryo Transfer 4:13-17.

24. OKAMOTO SH, HEALY DL, MORROW LM, ROGERS PAW, TROUNSON AO, WOOD EC (1987). Predictive value of plasma human chorionic gonadotrophin-subunit (ß-HCG) in diagnosing ectopic pregnancy following in vitro fertilization and embryo transfer (IVF-ET). Brit Med J 294:667-670.

25. CHAN CLK, CAMERON IT, FINDLAY JK, HEALY DL, LEETON JF, LUTJEN PJ, RENOU PM, ROGERS PA, TROUNSON AO, WOOD EC (1987). Oocyte donation and

IVF for hypergonadotropic hypogonadism: clinical state of the art. Obstet Gynecol Survey 42:350-362.

26. MURPHY CR, ROGERS PAW, LEETON J, HOSIE M, BEATON L, MACPHERSON A (1987). Surface ultrastructure of uterine epithelial cells in women with premature ovarian failure following steroid hormone replacement. Acta Anat 130:348-350.

27. KOLA I, TROUNSON A, DAWSON G, ROGERS P (1987). Tripronuclear human oocytes: altered cleavage patterns and subsequent karyotype analysis of embryos. Biol Reprod 37:395-401.

28. LEETON J, ROGERS P, CARO C, HEALY D, YATES C (1987). A controlled study between the use of gamete intrafallopian transfer (GIFT) and in vitro fertilization and embryo transfer in the management of idiopathic and male infertility. Fert Steril 48:605-607.

29. ROGERS PAW, MACPHERSON AM, BEATON LA (1988). Embryo implantation in the anterior chamber of the eye : effects on uterine allografts and the microvasculature. Ann NY Acad Sci 541:455-464

30. ROGERS PAW, MACPHERSON AM, BEATON L (1988). Vascular response in a non-uterine site to implantation-stage embryos in the rat and guinea-pig:in vivo and ultrastructural studies. Cell Tissue Res 254:217-224.

31. CAMERON IT, ROGERS PAW, SALAMONSEN LA, HEALY DL (1988). The endocrine requirements for implantation and early embryogenesis. J Reprod Fert 36:17-25.

32. ROGERS PAW (1988) In vitro fertilization statistics. Med. J. Aust. 148:206.

33. KOVACS GT, KING C, ROGERS P, WOOD C, BAKER HWG, YATES C (1989). In vitro fertilization, a practical option after failed artificial insemination with donor semen. Reprod. Fertil. Dev. 1:383-386.

34. ROGERS PAW, MURPHY CR, LEETON J, HOSIE M, BEATON L, MACPHERSON A (1989). An ultrastructural study of human uterine epithelium from a patient with a confirmed pregnancy. Acta Anat 135:176-179.

35. ROGERS PAW, MURPHY CR, CAMERON IK, LEETON J, HOSIE M, BEATON L, MACPHERSON A (1989). Uterine receptivity in women receiving steroid replacement therapy for premature ovarian failure: ultrastructural and endocrinological parameters. Human Reprod. 4:349-354.

36. CAMERON IT, ROGERS PAW, CARO C, HARMAN J, HEALY DL, LEETON JF (1989). Oocyte Donation: a review. Brit J Obstet Gynaecol 96:893-899.

37. LEETON J, ROGERS P, CAMERON I, CARO C, HEALY D. (1989). Pregnancy results following embryo transfer in women receiving low-dosage variable-length estrogen replacement therapy for premature ovarian failure. J. IVF and ET. 6:232-235.

38. MACPHERSON AM, ROGERS PAW, BEATON LA (1989). Vascular response in a non-uterine site to implantation stage embryos following xenogeneic transfers between the rat, mouse and guinea-pig. Cell Tiss. Res. 258:417-423.

39. CAMPO SM, ROGERS P, FINDLAY JK (1989). Sex hormone binding globulin in human follicular fluid and serum at the time of oocyte recovery. Reprod. Fertil. Dev. 1:289-297.

40. MURPHY CR, ROGERS PAW, KOVACS G, HAILES J, HOSIE M, BEATON L (1990). Post-Menopausal hormonal steroid therapy evaluated by scanning electron microscopy of the uterine epithelium. Acta Anat. 138:364-366.

41. ROGERS PAW, MACPHERSON A. (1990) In vivo microscopy of the rat endometrial subepithelial capillary plexus during the oestrous cycle and following ovariectomy. J. Reprod. Fert. 90:137-145.

42. ROGERS PAW, POLSON D, MURPHY CR, HOSIE M, SUSIL B, LEONI M. (1991) Correlation of endometrial histology, morphometry and ultrasound appearance following different stimulation protocols for IVF. Fertil. Steril. 55:583-587.

43. LEETON J, ROGERS P, KING C, HEALY D. (1991) A comparison of pregnancy rates for 131 donor egg transfers using either a sequential or fixed regime of steroid replacement therapy. Hum. Reprod. 6:299-301.

44. HOSIE MJ, MURPHY CR, ROGERS PAW, DWARTE DM. (1991) Morphometric comparison of uterine glandular epithelium in the early secretory phase from patients treated with different superovulatory drugs on an IVF programme. Acta Anat. 142:174-178.

45. SALAMONSEN LA, BUTT AR, MACPHERSON AM, ROGERS PAW, FINDLAY JK. (1992) Immunolocalization of the vasoconstrictor endothelin in human endometrium during the menstrual cycle and in umbilical cord at birth. Am. J. Obstet. Gynecol. 167:163-167.

46. ROGERS PAW, MURPHY CR, LEETON J, HOSIE M, BEATON L. (1992) Turner's syndrome patients lack tight junctions between uterine epithelial cells. Hum. Reprod. 7:883-885.

47. ROGERS PAW, MACPHERSON A, BEATON L (1992) Reduction in endometrial neutrophils in proximity to implanting rat blastocysts. J. Reprod. Fert. 96:283-288.

48. ROGERS PAW (1992) The early endometrial microvascular response during implantation in the rat. Reprod. Fertil. Dev. 4:261-264.

49. ROGERS PAW, MURPHY CR (1992) Morphometric and freeze fracture studies of human endometrium during the peri-implantation period. Reprod. Fertil. Dev. 4:265-269.

50. MURPHY CR, ROGERS PAW, LEETON J, HOSIE M, BEATON L (1992) Tight junctions of human uterine epithelial cells change during the menstrual cycle: A morphometric study. Acta Anat. 144:36-38.

51. ROGERS PAW, ABBERTON KM, SUSIL B (1992) Endothelial cell migratory signal production by human endometrium during the menstrual cycle. Hum. Reprod. 7:1061-1066.

52. SUBAKIR SB, ABBERTON KM, ROGERS PAW (1992) Endometrial angiogenic response in patients with menorrhagia. Med. J. Univ. Indonesia 1:71-73.

53. TAWIA SA, ROGERS PAW (1992) In vivo microscopy of the subepithelial capillary plexus of the endometrium of rats during embryo implantation. J. Reprod. Fert. 96:673-680.

54. POLSON DW, KRAPEZ JA, LEETON JF, ROGERS PA (1992) Randomized controlled study to assess the benefits of vaginal progesterone in an IVF/GIFT programme. Eur. J. Obstet. Gynaecol. 46:35-38.

55. AU CL, ROGERS PAW (1993) Immunohistochemical staining of von Willebrand factor in human endometrium during normal menstrual cycle. Hum. Reprod. 8:17-23.

56. TAWIA SA, BEATON LA, ROGERS PAW (1993) Immunolocalization of the cellular adhesion molecules, intercellular adhesion molecule-1 (ICAM-1) and platelet endothelial cell adhesion molecule (PECAM), in human endometrium throughout the menstrual cycle. Hum. Reprod. 8:175-181.

57. ROGERS PAW. (1993) Uterine receptivity. Reprod. Fertil. Dev. 4:645-652.

58. ROGERS PAW, AU CL, AFFANDI B (1993) Endometrial microvascular density during the normal menstrual cycle and following exposure to long-term levonorgestrel. Hum. Reprod. 8:1396-1404.

59. CRITCHLEY HOD, BAILEY DA, AU CL, AFFANDI B, ROGERS PAW (1993) Immunohistochemical sex steroid receptor distribution in endometrium from long-term subdermal levonorgestrel users and during the normal menstrual cycle. Hum. Reprod. 8:1632-1639.

60. WONODIREKSO S, AU CL, HADISAPUTRA W, AFFANDI B, ROGERS PAW (1993) Cytokeratins 8, 18 and 19 in endometrial epithelial cells during the normal menstrual cycle and in women receiving Norplant. Contraception 48:481-493.

61. MCCLURE N, MACPHERSON AM, ABBERTON K, HEALY DL, ROGERS PAW (1993) Human follicular fluid maturity and endothelial cell mitogenesis. Hum. Reprod. 10:1564-1569.

62. WOOD C, ROGERS PAW. (1993) Pregnancy after planned partial endometrial resection. Aust. N.Z. J. Obstet. Gynaecol. 33:316-318.

63. GOODGER (MACPHERSON) AM, ROGERS PAW (1993) Uterine endothelial cell proliferation before and after embryo implantation in rats. J. Reprod. Fertil. 99:451-457.

64. GOODGER (MACPHERSON) AM, ROGERS PAW (1994) Endometrial endothelial cell proliferation during the menstrual cycle. Hum. Reprod. 9:399-405

65. CRITCHLEY HOD, ABBERTON KM, TAYLOR N, HEALY, DL, ROGERS PAW (1994) Endometrial sex steroid receptor expression in women with menorrhagia. Brit. J. Obstet. Gynaecol. 101:428-434.

66. MCCLURE N, HEALY DL, ROGERS PAW, SULLIVAN J, BEATON L, HANING RV, CONNOLLY DT, ROBERTSON DM (1994) Vascular endothelial growth factor as capillary permeability agent in ovarian hyperstimulation syndrome. Lancet 344:235-236.

67. LEETON J, ROGERS P. (1994) Preparation of the endometrium for egg donation. J. Assist. Reprod. Genetics 10:459-461

68. MCCLURE N, MACPHERSON AM, HEALY DL, WREFORD N, ROGERS PAW (1994) An immunohistochemical study of the vascularization of the human Graafian follicle. Hum. Reprod. 9:1401-1405.

69. GOODGER (MACPHERSON) AM, ROGERS PAW, AFFANDI B (1994) Endometrial endothelial cell proliferation in longterm users of subdermal levonorgestrel. Human Reproduction 9: 1647-1651.

70. MCCLURE N, MACPHERSON AM, ABBERTON K, HEALY DL, WREFORD N, ROGERS PAW (1994) Human follicular fluid maturity and endothelial cell chemotaxis. Human Reproduction 9:1226-1230.

71. AU CL, AFFANDI B, ROGERS PAW (1994) Immunohistochemical staining of von Willebrand factor in endometrium of women during the first year of Norplant implants use. Contraception 50:477-489.

72. ABBERTON KM, ROGERS PAW (1995) Production of an endothelial cell migratory signal in rat endometrium during early pregnancy. Cell Tiss. Res. 279:215-220.

73. CRITCHLEY HOD, SUSIL B, KOOY J, MAMERS P, HEALY DL, ROGERS PAW (1995) Endometrial histology and vascular appearance following endometrial ablation. Gynaecological Endoscopy 4:27-33.

74. AFFANDI B, HADISAPUTRA W, ROGERS PAW (1995) Exploring the aetiology of increased endometrial bleeding in Norplant Users: the role of local factors? Med. J Indonesia 4:274-279.

75. KELLY FD, TAWIA SA, ROGERS PAW. (1995) Immunohistochemical characterisation of human endometrial microvascular basement membrane components during the normal menstrual cycle. Hum. Reprod. 10:268-276.

76. THOMAS T, MACPHERSON AM, ROGERS PAW (1995) Ceruloplasmin gene expression in the rat uterus. Biochimica et Biophysica Acta. 1261:77-82.

77. WINGFIELD M, MACPHERSON A, HEALY DL, ROGERS PAW (1995) Cell proliferation is increased in the endometrium of women with endometriosis. Fertility and Sterility 64:340-346.

78. GOODGER (MACPHERSON) AM, ROGERS PAW (1995) Blood vessel growth in the endometrium. Microcirculation 2:329-343.

79. MARSH MM, BUTT AR, RILEY SC, ROGERS PAW, SUSIL B, AFFANDI B, FINDLAY JK, SALAMONSEN LA (1995) Immunolocalization of endothelin and neutral endopeptidase in the endometrium of users of subdermally implanted levonorgestrel (Norplant). Hum. Reprod. 10:2584-2589.

80. GOODGER (MACPHERSON) AM, ROGERS, PAW. (1995) Blood vessel growth and endothelial cell density in rat endometrium. J. Reprod. Fert. 105:259-261.

81. ROGERS PAW (1995) Current studies on human implantation: a brief overview. Reprod. Fertil. Dev. 7: 1395-1399.

82. ROGERS PAW, HOSIE MJ, ORTIS A, SUSIL B, LEETON J, MURPHY CR (1996) Uterine glandular area during the menstrual cycle and the effects of different in-vitro fertilization related hormonal treatments. Hum. Reprod. 11:376-379.

83. ABBERTON KM, TAYLOR NH, HEALY DL, ROGERS PAW (1996) Vascular smooth muscle alpha actin distribution around endometrial arterioles during the menstrual cycle: increased expression during the perimenopause and lack of correlation with menorrhagia. Hum. Reprod. 11: 204-211.

84. LAU TM, AFFANDI B, ROGERS PAW (1996) Immunohistochemical detection of cathepsin D in endometrium from long-term subdermal levonorgestrel users and during the normal menstrual cycle. Mol. Hum. Reprod. 2:233-237.

85. KOOY J, TAYLOR NH, HEALY DL, ROGERS PAW. (1996) Endothelial cell proliferation in the endometrium of women with menorrhagia and in women following endometrial ablation. Hum. Reprod. 11:1067-1072.

86. ROGERS, PAW. (1996) Structure and function of endometrial blood vessels. Hum. Reprod. Update 2:57-62.

87. CLARK DA,WANG S, ROGERS PAW, VINCE G, AFFANDI B. (1996) Endometrial lymphomyeloid cells in abnormal uterine bleeding due to levonorgestrel (Norplant). Hum. Reprod. 11:1438-1444.

88. HICKEY M, LAU TM, RUSSELL P, FRASER I, ROGERS PAW (1996) Microvascular density in conditions of endometrial atrophy. Hum. Reprod. 11: 2009-2103.

89. PALMER JA, LAU TM, HICKEY M, ROGERS PAW. (1996) Immunohistochemical study of endometrial microvascular basement membrane components in women using Norplant. Hum. Reprod.11:2142-2150.

90. ROGERS PAW, LEDERMAN F, KOOY J, TAYLOR NH, HEALY DL (1996) Endometrial vascular smooth muscle oestrogen and progesterone receptor distribution in women with and without menorrhagia. Hum. Reprod. 11:2003:2008.

91. WONODIREKSO S, HADISAPUTRA W, AFFANDI B, SIREGAR B, ROGERS PAW. (1996) Cytokeratin 8, 18 and 19 in endometrial epithelium of Norplant and norethisterone enanthate (NET-EN) injectable progestogen contraceptive users. Hum. Reprod. 11:144-149.

92. ROGERS PAW. (1996) Endometrial vasculature in Norplant® users. Hum. Reprod. 11:45-50.

93. WITJAKSONO J, LAU TM, AFFANDI B, ROGERS PAW. (1996) Estrogen treatment for increased bleeding in Norplant users. Preliminary results. Hum. Reprod. 11:109-114.

94. LAU TM, WITJAKSONO J, ROGERS PAW. (1996) Progesterone receptor in normal and Norplant endometrium. Hum. Reprod. 11:90-94.

95. HADISAPUTRA W, AFFANDI B, WITJAKSONO J, ROGERS PAW. (1996) Endometrial biopsy collection from women receiving Norplant®. Hum. Reprod. 11:31-33.

96. LAU TM, WITJAKSONO J, AFFANDI B, ROGERS PAW. (1996) Expression of progestrone receptor mRNA in the endometrium during the normal menstrual cycle and in Norplant users. Hum. Reprod. 11:2629-2634.

97. ORRE M, ROGERS PAW (1998) Reduced vascular basement membrane immunostaining in mucinous tumours of the ovary. Int J Cancer 79:139-143.

98. ROGERS PAW. (1998) To what extent does endometrial receptivity influence the outcome of assisted reproductive technology? J. Ass. Reprod. & Gen. 15:177-179.

99. WONODIREKSO S, HADISAPUTRA W, AFFANDI B, SIREGAR B, ROGERS PAW. (1998) Cytokeratin 8, 18 and 19 expressions, epithelial shedding, and stromal extravasation in endometrium of norethisterone enanthate (NET-EN) progestogen contraceptive users. Medical Journal of Indonesia. 7:16-24.

100. HII L, ROGERS PAW (1998) Endometrial vascular and glandular expression of intergrin αvβ3 in women with and without endometriosis. Hum. Reprod. 13:1030:1035.

101. ORRE M, LOFTI-MIRI M, MAMERS P, ROGERS PAW (1998) Increased microvessel density in mucinous compared with malignant serous and benign tumours of the ovary. Brit. J. Cancer 77: 2204-2209.

102. HEALY DL, ROGERS PAW, HII L, WINGFIELD M (1998) Angiogenesis: a new theory for endometriosis. Hum Reprod Update 4:736-740.

103. LAU TM, AFFANDI B, ROGERS PAW (1998) The effects levonorgestrel implants on vascular endothelial growth factor expression in the endometrium. Mol Hum Reprod 5:57-63.

104. ROGERS PAW, LEDERMAN F, TAYLOR N (1998) Endometrial microvascular growth in normal and dysfunctional states. Hum Reprod Update 4:503-508.

105. ORRE M, ROGERS PAW (1999) VEGF, VEGFR-1 and VEGFR-2, microvessel density and endothelial cell proliferation in tumours of the ovary. Int J Cancer 84:101-108.

106. VINCENT AL, MALAKOOTI N, ROGERS PAW, AFFANDI B, SALAMONSEN LA. (1999) Endometrial breakdown in women using Norplant is associated with migratory cell expression of matrix metalloproteinase-9 (gelatinase B). Hum Reprod 14:807-815.

107. ORRE M, ROGERS PAW (1999) Macrophages and microvessel density in tumours of the ovary. Gyn Oncol 73:47-50.

108. ABBERTON KM, TAYLOR NH, HEALY DL, ROGERS PAW. (1999) Vascular smooth muscle cell proliferation in arterioles of the human endometrium. Hum Reprod 14:1072-1079.

109. ROSAMILIA A, CANN L, DWYER P, SCURRY J, ROGERS PAW (1999) Bladder microvasculature in women with interstitial cystitis. J Urology 161:1865-1870.

110. GARGETT CE, LEDERMAN F, LAU TM, TAYLOR N, ROGERS PAW (1999) Lack of correlation between VEGF production and angiogenesis in the human endometrium. Hum Reprod 14:2080-2088.

111. ROGERS PAW, GARGETT CE (1999) Endometrial Angiogenesis. Angiogenesis 2:287-294.

112. ABBERTON KM, HEALY DL, ROGERS PAW (1999) Expression of the tyrosine kinase receptors Tie-1 and Tie-2 on the microvasculature of the human endometrium. Hum Reprod (in press)

113. WINGFIELD M, MACPHERSON AM, HEALY DL, ROGERS PAW. (1999) Endothelial cell chemotaxis in response to endometrium-conditioned medium from women with and

without endometriosis. Angiogenesis (Submitted)

114. ORRE M, SUSIL B, ROGERS PAW (1999) Microvessel density and vascular basement membrane immunostaining in tumours of the breast. Angiogenesis (In press)

115. GARGETT CE, BUCAK K, ROGERS PAW. (1999) Isolation, characterisation and long-term culture of human myometrial microvascular endothelial cells. Hum Reprod (In press)

116. ABBERTON KM, HEALY DL, ROGERS PAW (1999) Smooth muscle alpha actin and myosin heavy chain expression in the vascular smooth muscle cells surrounding endometrial arterioles. Hum Reprod (submitted)

117. ACHEN MG, WILLIAMS RA, MINEKUS M, STENVERS K, ROGERS PAW, LEDERMAN F, ROUFAIL S, STACKER SA. (1999) Localization of vascular endothelial growth factor-D in malignant melanoma indicates a role in tumor angiogenesis. Cancer Res (submitted)

118. LEETON J, PLATTEAU P, ROGERS PAW. (1999) Hormone replacement treatment in donor egg cycles. Hum Reprod (submitted)

119. CASEY R, ROGERS PAW, VOLLENHOVEN BJ. (1999) An immunohistochemical analysis of fibroid vasculature. Hum Reprod (submitted)

120. GARGETT CE, LEDERMAN F, HERYANTO B, ROGERS PAW (1999) Focal vascular endothelial growth factor correlates with angiogenesis in human endometrium. Am J Path (submitted)

121. HAMPTON AL, ROGERS PAW, AFFANDI B, SALAMONSEN LA. (1999) Expression of the chemokines, monocyte chemotactic protein (MCP)-1 and MCP-2 in endometrium of normal women and Norplant® users does not support a central role in macrophage infiltration into endometrium. (in preparation)

122. VINCENT AJ, ZHANG J, OSTOR A, ROGERS PAW, AFFANDI B, KOVACS G, SALAMONSEN LA (1999) Matrix metalloproteinases and mast cells: A role in abnormal uterine bleeding associated with progestin-only contraceptives? Hum Reprod (In preparation)

NON-REFEREED CHAPTERS, REVIEWS AND ARTICLES

123. WELLS RT, HORTON DR, ROGERS P (1982). Thylacoleo carnifex Owen (Thylacoleonidae) : marsupial carnivore? In: Carniverous Marsupials. Ed. Archer M, A.N.U. Press. pp. 573-586.

124. GANNON BJ, BROWNING J, ROGERS PAW, HARPER B (1983) Microvascular organization in the intestine. In: Microcirculation of the Alimentary Tract. Eds. Koo A, Lam SK, Smaje LH. World Scientific, Singapore, pp. 39-55.

125. ROGERS PAW, GANNON BJ (1984). Uterine microvascular events prior to and during implantation in the rat. Prog Microcirc Res II pp. 48-53.

126. TROUNSON A, HOPPEN H-O, LUTJEN PJ, MOHR LR, ROGERS PAW, SATHANANTHAN AH (1985). In vitro fertilization: the state of the art. In: Gamete Quality and Fertility Regulation. Eds. Rolland R, Heineman MJ, Hillier SG, Vemer H. Excerpta Medica, Amsterdam pp. 325-343.

127. ROGERS PAW, TROUNSON AO (1986). IVF the future. In: In Vitro Fertilization : Past, Present and Future. Eds. Fishel S, Symonds D. IRL Press, Oxford, pp. 229-245.

128. HEALY DL, OKAMOTO S, MORROW L, THOMAS A, JONES M, McLACHLAN V, BESANKO M, MARTINEZ F and ROGERS P (1987). Contributions of in vitro fertilization to knowledge of the reproductive endocrinology of the menstrual cycle. In: Bailliére's Clinical Endocrinology and metabolism. Ed. Burger HG. Vol 1, No1, pp. 133-152.

129. ROGERS P, LEETON J, CAMERON I, MURPHY C, HEALY D, LUTJEN P (1988). Oocyte donation. In: Clinical In Vitro Fertilization. Eds. Wood C, Trounson A. 2nd Edition, Springer-Verlag, London. pp. 143-154.

130. JONES HW, ROGERS PAW (1988). Results from in vitro fertilization. In: Clinical In Vitro Fertilization. Eds. Wood C, Trounson A. 2nd Edition, Springer-Verlag, London. pp. 51-62.

131. TROUNSON AO, ROGERS PAW, KOLA I, SATHANANTHAN H (1989). Fertilization, development and implantation. In: Textbook of Obstetrics. Eds. Turnbull A, Chamberlain G. Churchill Livingstone, Edinburgh, pp.49-66.

132. ROGERS PAW, MURPHY CR. (1989). Uterine receptivity for implantation: Human studies. In Blastocyst Implantation. Ed. Yoshinaga K., Serono Symposia, Adams Publishing Group, Boston. pp. 231-238.

133. ROGERS PAW (1989). Infertility and IVF techniques. In: Disease and Society. A Resource Book. Compiled by Ruth Dirks. Australian Acadamy of Science. pp. 5.19-5.20.

134. JAMES JM, ROGERS P, SPATE AP. (1989) Genesis of the caves of the Nullabor plain, Australia. Proc. International Union of Speleological Congresses, Budapest, August 1989.

135. ROGERS PAW, AU CL, AFFANDI B (1992) Effects of Norplant on the endometrial vasculature. In: Steroid Hormones and Uterine Bleeding. Eds Alexander NJ, d'Arcangues C. AAAS Press, Washington. pp 59-66.

136. ROGERS PAW. (1993) Uterine receptivity. In: Handbook of In Vitro Fertilization. Gardner D, Trounson AO, Eds, CRC Press, Boca Raton, Florida. pp. 263-285.

137. ROGERS PAW (1995) Current basic scientific studies on the mechanisms of progestogen induced endometrial bleeding. In: Advances in Human Reproduction. Eds. FA Moeloek, B Affandi and AO Trounson. Parthenon Publishing, UK. Section 5, pp217-224.

138. TROUNSON AO, ROGERS PAW, KOLA I, SATHANANTHAN H (1995). Fertilization, early development and implantation. In: Turnbull's Obstetrics. Second Edition. Eds. Chamberlain G. Churchill Livingstone, Edinburgh. Section 1:3, pp25-43.

139. ROGERS PAW (1995) Maternal age effects on the endometrium. 2nd Joint Symposium. Review of the major success factors in IVF and the treatment of endometriosis. Monash IVF & Cha General Hospital, Seoul, Korea. April 29-30th. pp 177-179.

140. ROGERS PAW, LEDERMAN F, KOOY J, TAYLOR NH, HEALY DL (1996) Vascular smooth muscle oestrogen and progesterone receptor distribution in the endometrium of women with and without menorrhagia. In: 6th World Congress for Microcirculation. Eds. K. Messmer, WM Kübler. Monduzzi Editore. pp 803-807.

141. ABBERTON KM, HEALY DL, ROGERS PAW (1996) Vascular smooth muscle cell proliferation in the human endometrium. In: 6th World Congress for Microcirculation. Eds. K. Messmer, WM Kübler. Monduzzi Editore. pp 791-795.

142. ORRE M, HEALY DL, MC CLURE N, ROBERTSON D, ROGERS PAW (1997) Vascular endothelial growth factor is an intraovarian regulator of angiogenesis and corpus luteum formation. In: FSH Action and Intraovarian Regulation Fauser B.C.J.M. Ed. The Parthenon Publishing Group. New York. pp167-175.

143. ROGERS PAW (1998) Menstruation. In: Estrogens and progestogens in clinical practice. Eds. I. Fraser, R. Jansen, R. Lobo and M. Whitehead. Churchill Livingstone, Edinburgh. U.K.

144. ROGERS PAW (1998) The endometrial vascular bed. In: Clinical disorders of the endometrium and menstrual cycle. Eds. I.T. Cameron, I.S. Fraser and S.K. Smith. Oxford University Press, New York, USA. pp 31-45.

145. TSALTAS J, ROGERS PAW, GARGETT C, HEALY DL (1998) Excessive angiogenesis: A new theory for endometriosis. Curr Obs & Gyn (In press) 8:4;

146. GARGETT C, TSALTAS J, ROGERS PAW, TAYLOR N, LAWRENCE M, HEALY DL. (1999) Excessive angiogenesis: a new theory for endometriosis. In: Understanding Endometriosis. Proceedings of the VI World Congress on Endometriosis. Edited by A. Lemay and R. Maheux.

147. ROGERS PAW (1999) Mechanisms of progestin-induced endometrial bleeding. Gyn Forum 4:17-21.

148. ROGERS PAW, LEETON J (1999) Uterine receptivity and embryo transfer. In: Handbook of In Vitro Fertilization 2nd edition. Gardner D, Trounson AO, Eds. 21:499-

528.

149. ROGERS PAW, HII L (1999) Endometrial immunostaining for v 3 integrin. Letter to Editor. Hum Reprod (In press).

150. ROGERS PAW (1999) Endometriosis: why and how? Harwood Academic Publishers gmbh. In: Hormones and Women's Health: The Reproductive Years. (In press)

ABSTRACTS

1. GANNON BJ, ROGERS PAW (1978). Gill microanatomy and microcirculation in the southern bluefin tuna. Aust Soc Fish Biol 5th Annual Conference.

2. GANNON BJ, ROGERS PAW, O'BRIEN PE (1980). Two capillary plexuses in human intestinal villi. Micron 11, Suppl 1:25.

3. GANNON BJ, GORE RW, ROGERS PAW (1980). Dual blood supplies to intestinal villi of rabbit and rat. Microvasc Res 19:247.

4. ROGERS PAW (1980). Vascular and microvascular anatomy of the crayfish gill (Jasus novaehollandiae). Aust Soc Fish Biol 7th Annual Conference.

5. GANNON BJ, ROGERS PAW, GORE RW (1981). Is there an anatomical basis for a vascular counter current mechanism in rabbit and human intestinal villi? Proc Anat Soc Aust NZ J Anat 132:315.

6. ROGERS PAW, MURPHY CR, GANNON BJ (1981). Microvasculature of the rat uterus during early pregnancy. Proc 13th Aust Conf Exp Path.

7. ROGERS PAW, MURPHY CR, GANNON BJ (1982). Absence of capillaries in the endometrium surrounding the implanting rat blastocyst. Proc 7th Aust Conf Electron Microscopy p. 75.

8. ROGERS PAW, MURPHY CR, GANNON BJ (1982). Changes in the microvasculature of the rat uterus during implantation. Proc 7th Aust Conf Electron Microscopy p. 39.

9. ROGERS PAW, MURPHY CR, SQUIRES KR, MacLENNAN AH (1982). The effects of relaxin on the antimesometrial positioning of the rat blastocyst for implantation. Proc 1st Ann Conf Fert Soc Aust 1:60.

10. ROGERS PAW, MURPHY CR, GANNON BJ (1983). Effects of an IUD on the spatial organisation of the uterine vasculature in pregnant rats. Proc Anat Soc Aust NZ, J Anat 136:646-647.

11. MacLENNAN AH, ROGERS PAW, KIERIN JFP (1983). The role of relaxin in implantation. Aust Perinatal Soc Inaugural Meeting.

12. ROGERS PAW, GANNON BJ (1983). Uterine microvascular events prior to and during implantation in the rat. Second Aust NZ Symp Microcirc Abstracts Vol II:11.

13. ROGERS PAW, MURPHY CR, GANNON BJ (1983). Effects of an IUCD on endometrial morphology around the time of implantation in the rat. Aust Soc Rep Biol Proc 15th Ann Conf, pp. 63.

14. ROGERS PAW, MILNE BJ, TROUNSON AO (1984). Embryo viability and uterine receptivity in human IVF. Aust Soc Rep Biol Proc 16th Ann Conf, pp. 39.

15. KOVACS GT, ROGERS PAW (1984). IVF - a practical option when AID fails. Proc 3rd Ann Conf Fert Soc Aust, pp. 2.

16. ROGERS PAW, MILNE BJ, TROUNSON AO (1984). The effect of stimulation to produce multiple follicular development on embryo viability and uterine receptivity in human IVF. Proc 3rd Ann Conf Fert Soc Aust, pp. 32.

17. LUTJEN J, CARO CM, JESSUP D, ROGERS P, TROUNSON A (1984). Some factors affecting success rates of IVF. Proc 3rd Ann Conf Fert Soc Aust (Poster F).

18. ROGERS PAW (1985). Culture media : quality control. Aust Soc for Reprod Biol. Embryo Transfer Satellite Symposium, 25th August 1985. Invited Lecture.

19. ROGERS PAW (1985). Embryo viability and uterine receptivity. 4th World Conference on IVF, Melbourne, pp 133. Plenary Lecture.

20. ROGERS PAW, HARMAN J, McDONALD J, FIELD P, CROFT M, BARLOW A (1985). The use of previous menstrual cycle length history to individualize ovulation induction for IVF. 4th World Conference on IVF, Melbourne, pp 164.

21. HOWLETT D, ROGERS PAW (1985). The use of hyaluronidase to assess oocyte maturity in an in vitro fertilization programme. 4th World Conference on IVF, Melbourne, pp. 47.

22. MARTINEZ F, ROGERS PAW, TROUNSON AO (1985). An analysis of ectopic pregnancies in the Monash IVF programme. 4th World Conference on IVF, Melbourne, Poster 13.

23. KOVACS GT, ROGERS PAW (1985). The assessment of in vitro fertilization success rates by life-table analysis. 4th World Conference on IVF, Melbourne, pp. 18.

24. ROGERS PAW, MACPHERSON A, BEATON L (1986). Embryo implantation in the anterior chamber of the rat eye following transplantation of uterine tissue. Gordon Conference on Mammalian Genital Tract, Plymouth, New Hampshire, July 7-11, 1986.

25. ROGERS PAW, MACPHERSON A, BEATON L (1986). Embryo-uterine interaction using the anterior eye chamber in the rat. Aust Soc Reprod Biol, Proc 18th Annual Conference, pp. 97.

26. CHIAPPAZZO L, ROGERS P, KIRBY C, TROUNSON A (1986). The use of human amniotic fluid as an embryo culture medium for human IVF. Aust Soc Reprod Biol, Proc 18th Annual Conference, pp. 35.

27. HEALY DL, BESANKO M, McLAUGHLIN V, MORROW L, OKAMOTO S, ROGERS P, THOMAS T (1986). Buserelin in management of unsatisfactory superovulation response in an IVF programme. Endocrine Soc Aust, September 1986.

28. ROGERS PAW, MACPHERSON A, BEATON L (1986). In vivo study of uterine response to embryo implantation using the anterior chamber of the eye in the rat. Fertility Society of Australia, Adelaide, December 3-6, Clin. Reprod. Fertil. 4:449-450.

29. MURPHY CR, ROGERS PAW, LEETON J, HOSIE M, BEATON L, MACPHERSON A (1986). Endometrial surface ultrastructure in patients with premature ovarian failure following steroid hormone replacement therapy. Fertility Society of Australia, Adelaide, December 3-6, Clin. Reprod. Fertil. 4:449-450.

30. OKAMOTO SH, HEALY DL, HOWLETT DT, ROGERS PAW, TROUNSON AO, WOOD EC (1986). An analysis of plasma estradiol concentrations during clomiphene citrate-human menopausal gonadotrophin stimulation in an in vitro fertilization-embryo transfer programme. Fertility Society of Australia, Adelaide, December 3-6, pp.B1.

31. ROGERS PAW, MACPHERSON A, BEATON L (1987). Microvascular events during implantation. 4th Aust. NZ Symp. Microcirculation, Sydney, pp. 29.

32. ROGERS PAW, MACPHERSON A, BEATON L (1987). Embryo implantation in the anterior chamber of the eye : effects on uterine allografts and the microvasculature. 5th World Conf. IVF, Norfolk, USA. Abstract OC-419.

33. ROGERS PAW, MURPHY CR, LEETON J, HOSIE M, BEATON L, MACPHERSON A (1987). Ultrastructure of human endometrial epithelium following steroid replacement for premature ovarian failure. 5th World Conf. IVF, Norfolk, USA. Abstract AP-615.

34. OKAMOTO SH, HEALY DL, MORROW LM, ROGERS PAW, TROUNSON AO, WOOD EC (1987). Predictive value of plasma human chorionic gonadotrophin ß-subunit (ß-HCG) in diagnosing ectopic pregnancy following in vitro fertilization and embryo transfer. 5th World Conf. IVF, Norfolk, USA. Abstract OC-434.

35. GIANAROLI L, TROUNSON A, SERACCHIALI R, ROGERS PAW, FERRARETTI AP, KIRBY C, CHIAPPAZZO L, FLAMIGNI C (1987). Fertilization and culture in physiological fluids : a major improvement in IVF success rates in a multicentre trial. 5th World Conf. IVF, Norfolk, USA. Abstract PP-101.

36. KOLA I, TROUNSON A, DAWSON G, ROGERS P (1987). Tripronuclear human oocytes : altered cleavage patterns and subsequent karyotypic analysis of embryos. Aust Soc Reprod Biol Proc 19th Ann Conf, pp.49.

37. ROGERS PAW, MACPHERSON A, BEATON L (1987). Ultrastructural response of endothelial cells to embryo implantation in a non-uterine site. Fertility Society of Australia, November 11-14, pp. 048.

38. CAMERON IT, ROGERS PAW, BESANKO M, MACLACHLAN VB, O'SHEA FC, HEALY DL, LEETON J (1987). Artificial menstrual cycles in agonadal women : an assessment of steroid replacement therapy. Fertility Society of Australia, November 11-14, pp. 050.

39. MURPHY CM, ROGERS PAW, LEETON J, CAMERON I, HOSIE M, BEATON L, MACPHERSON A (1987). Scanning electron microscopy of human uterine epithelium after varying hormonal replacement regimes. Fertility Society of Australia, November 11-14, pp P17.

40. ROGERS PAW, MACPHERSON A and BEATON L (1988). Vascular response following the interspecies transfer of embryos to a non-uterine site. Gordon Research conference on Reproductive Tract Biology. Wolfboro, New Hampshire, July 3-8.

41. ROGERS PAW, MACPHERSON A and BEATON L (1988). Interspecies transfer of preimplantation embryos to a non-uterine site. Fertility Society of Australia, August 28-Sept. 1.

42. CAMERON IT, ROGERS PAW, HEALY DL and LEETON J (1988). The development of a flexible steroid replacement schedule for agonadal women undergoing in-vitro fertilization using donated oocytes. Fertility Society of Australia, August 28-Sept. 1.

43. MURPHY CR, ROGERS PAW, KOVACS GT, HAILES J, HOSIE M, BEATON L and MACPHERSON A (1988). Evaluation of exogenous hormonal therapy on postmenopausal patients by scanning electron microscopy. Fertility Society of Australia, August 28-Sept. 1.

44. HOSIE M, MURPHY CR, ROGERS PAW, LEETON J and HEALY D (1988). A morphometric scoring system for scanning electron microscopic data of the human endometrium. Fertility Society of Australia, August 28-Sept. 1, Poster 13.

45. OKAMOTO S, HEALY DL, MORROW LM, ROGERS PAW, TROUNSON AO (1988). Human chorionic gonadotrophin ß-subunit (ß-hCG) concentrations predict pregnancy outcome following IVF-ET. 8th International Congress of Endocrinology, Kyoto, Japan

46. ROGERS PAW, MACPHERSON AM and BEATON LA (1989). The response of iridial microvessels to allogeneic and xenogeneic implantation stage embryos. Progress in Microcirculation Research. Proceedings of the Fifth Australian and New Zealand Microcirculation Symposium. Canberra. pp 1-2

47. ROGERS PAW (1989). Endometrial microcirculation. Progress in Microcirculation Research. Proceedings of the Fifth Australian and New Zealand Microcirculatin Symposium. Canberra. pp 83-84.

48. CAMERON IT, ROGERS PAW, CARO C, LEETON JF (1989). Oocyte donation and in vitro fertilisation for agonadal women. British Congress of Obstetrics and Gynaecology. July.

49. ROGERS PAW. (1989) Vascular density of the rat endometrial subepithelial capillary plexus during the oestrus cycle and following ovariectomy. Australian Society Reproductive Biology, 21st Annual Conference. Melbourne, September 27 - 29 pp19.

50. HOSIE MJ, MURPHY CR, ROGERS PAW, LEETON J, BEATON L. (1989) A freeze fracture study of the tight junctions of the uterine luminal epithelium from patients on hormone replacement therapy on an IVF programme. Fertility Society of Australia, 8th Annual Conference, Canberra. November 30 - December 2. pp 72.

51. HOSIE MJ, MURPHY CR, ROGERS PAW, HEALY DL, LEETON J, BEATON L. (1989) A morphometric analysis of glandular epithelium from patients in hormone replacement therapy in an IVF programme. Fertility Society of Australia, 8th Annual Conference, Canberra. November 30 - December 2. pp 71.

52. ROGERS PAW, POLSON D, LEONI M, SUSIL B. (1989) Correlation of endometrial histology with ultrasound appearance following different stimulation protocols for IVF. Fertility Society of Australia, 8th Annual Conference, Canberra. November 30 - December 2. pp 35.

53. KRAPEZ JA, POLSON DW, ROGERS PAW. (1989) A randomised controlled trial of luteal support with vaginal progesterone pessaries in an IVF/GIFT programme. Fertility Society of Australia, 8th Annual Conference, Canberra. November 30 - December 2. pp 36.

54. KING CM, ROGERS PAW, LEETON JF, POLSON DW, HEALY DL.(1989) A comparison of pregnancy rates for donor egg patients receiving two types of steroid replacement schedules. Fertility Society of Australia, 8th Annual Conference, Canberra. November 30 - December 2. pp 15.

55. POLSON DW, KING CM, ROGERS PAW, HEALY DL, RENOU P, LEETON JF. (1989) The Monash IVF donor oocyte programme - Obstetric and neonatal outcome. Fertility Society of Australia, 8th Annual Conference, Canberra. November 30 - December 2. pp 18.

56. ROGERS PAW (1989) Uterine receptivity for implantation. Proc. Embryology Symp., Fert. Soc. Aust., Canberra, 28 November, pp.27-29.

57. ROGERS PAW, MACPHERSON AM, BEATON L. (1990) Loss of neutrophils from rat endometrium during implantation. Proc 29th Nat Sci Conf Aust Soc Med Res, Lorne, 9-12 Dec, pp70.

58. ABBERTON KM, ROGERS PAW. (1990) A signal for vascular endothelial cell migration in rat endometrium. Proc 29th Nat Sci Conf Aust Soc Med Res, Lorne, 9-12 Dec, pp69.

59. ROGERS PAW, MACPHERSON AM. (1991) In vivo microscopy of rat endometrial microcirculation during the oestrous cycle, following ovariectomy, and at embryo implantation. Prog. Microcirc. Res., Proc. 6th Aust. NZ Symposium, 3-6 Feb, pp51-53.

60. ABBERTON KM, ROGERS PAW. (1991) A migratory signal for vascular endothelial cells in the endometrium of the rat. Prog. Microcirc. Res., Proc. 6th Aust. NZ Symposium, 3-6 Feb, pp55-57.

61. MACPHERSON AM, ROGERS PAW. (1991) Permeability of the rat endometrial subepithelial capillary plexus to different molecular weight fluorescent-labeled dextrans after a single dose of oestradiol. Prog. Microcirc. Res., Proc. 6th Aust. NZ Symposium, 3-6 Feb, pp58-60.

62. ROGERS PAW, ABBERTON KM. (1991) Evidence for a novel, steroid regulated, angiogenic factor in human endometrium. 3rd Aust. Menopause Soc. Congress, Adelaide, April 21-24.

63. ROGERS PAW (1991) The early endometrial microvascular response during implantation in the rat. NSF-DITAC Cooperative Workshop on "Successful maternal recognition of pregnancy: Signaling between the conceptus and maternal system." University of Hawaii, Honolulu, July 1-3rd.

64. ROGERS PAW, MURPHY CR (1991) Morphometric and freeze fracture studies of human endometrium during the peri-implantation period. NSF-DITAC Cooperative Workshop on "Successful maternal recognition of pregnancy: Signaling between the conceptus and maternal system." University of Hawaii, Honolulu, July 1-3rd.

65. MCKAY SA, ROGERS PAW. (1991) In vivo microscopy of rat endometrial microcirculation at embryo implantation. 5th World Congress for Microcirculation, Louisville, Kentucky, USA, August 31st- September 5th, Abstract 510.

66. AU CL, ABBERTON KM, ROGERS PAW. (1991) Local regulation of angiogenesis and endothelial cell factor VIII levels in human endometrium. 5th World Congress for Microcirculation, Louisville, Kentucky, USA, August 31st- September 5th, Abstract 800.

67. MCKAY SA. ROGERS PAW. (1991) In vivo microscopy of the endometrial microcirculation at embryo implantation in the rat. Australian Society Reproductive Biology, Proceedings 23rd Annual Conference. Sydney, September 30 - October 2nd, pp1.

68. AU CL, ABBERTON KM, ROGERS PAW. (1991) Local regulation of angiogenesis and endothelial cell factor VIII levels in human endometrium. Australian Society Reproductive Biology, Proceedings 23rd Annual Conference. Sydney, September 30 - October 2nd, pp2.

69. ORTIS A, HOSIE M, MURPHY CR, ROGERS PAW. (1991) Turner's syndrome patients have underdeveloped uterine glands. Australian Society Reproductive Biology, Proceedings 23rd Annual Conference. Sydney, September 30 - October 2nd, pp13.

70. FINDLAY JK, BUTT AR, MACPHERSON AM, ROGERS PAW, SALAMONSEN LA. (1991) Immunolocalization of the vasoconstrictor, endothelin, in human endometrium throughout the menstrual cycle. Australian Society Reproductive Biology, Proceedings 23rd Annual Conference. Sydney, September 30 - October 2nd, pp15.

71. ROGERS PAW, BEATON LA, MCKAY TAWIA SA. (1991) Immunolocalization of cellular adhesion molecules in human endometrium during the menstrual cycle. Fertility Society of Australia, 10th Annual Conference, Lorne, Victoria. November 18-22nd. pp 7.

72. CALDERON I, LEONI M, KIOULAFAS A, BEATON L, SUSIL B, LEETON J, ROGERS P. (1991) Endometrial histology and ultrasound appearances at time of oocyte retrieval in superovulated patients. Fertility Society of Australia, 10th Annual Conference, Lorne, Victoria. November 18-22nd. pp 3.

73. SUBAKIR SB, ABBERTON KM, ROGERS PAW. (1991) Endometrial angiogenic response in patients with menorrhagia. Fertility Society of Australia, 10th Annual Conference, Lorne, Victoria. November 18-22nd. pp 60.

74. ROGERS PAW. (1991) Norplant and the endometrium. Fertility Society of Australia, 10th Annual Conference, Lorne, Victoria. November 18-22nd.

75. ROGERS PAW. (1991) Uterine receptivity. Serono Symposium on Oocyte Donation, Melbourne, 22-24th November.

76. ROGERS PAW. (1991) Local regulation of human endometrial microvascular function. Proceedings of the 30th National Scientific Conference, Australian Society for Medical Research, Canberra, 15-18th December, pp 67.

77. ROGERS PAW, AU CL, AFFANDI B (1992) Effects of Norplant on the endometrial vasculature. NIH meeting on "Exogenous hormones and dysfunctional uterine bleeding", Bethesda, USA, May 4-6th, 1992.

78. ROGERS PAW (1992) Basic mechanisms of endometrial bleeding. Australian Menopause Society, 3rd Congress, Melbourne, April 5-8th. pp 23.

79. ABBERTON KM, TAYLOR N, SUSIL B, ROGERS PAW (1992) A comparison of endometrial microvascular Factor VIII related antigen and collagen IV between women with and without perimenopausal bleeding. Australian Menopause Society, 3rd Congress, Melbourne, April 5-8th. pp 53.

80. MACPHERSON AM, ROGERS PAW (1992) Proliferating endothelial cells in the endometrium of early pregnant rats. 17th European Conference on Microcirculation, London, 5-10th July.

81. AU CL, AFFANDI B, ROGERS PAW (1992) Changes in blood vessel density and endothelial von Willebrand factor levels in the endometrium of women receiving subcutaneous levonorgestrel implants - Norplant. Australian Society for Reproductive Biology, Proceedings 24th Annual Conference. Adelaide, September 27-30th, p122.

82. TAWIA SA, BEATON LA, ROGERS PAW (1992) Expression of cellular adhesion molecules in human endometrium throughout the menstrual cycle. Australian Society for

Reproductive Biology, Proceedings 24th Annual Conference. Adelaide, September 27-30th, p123.

83. MACPHERSON AM, ROGERS PAW (1992) Proliferating endothelial cells in the endometrium of early pregnant rats. Australian Society for Reproductive Biology, Proceedings 24th Annual Conference. Adelaide, September 27-30th, p34.

84. CRITCHLEY HOD, AU CL, BAILEY DA, AFFANDI B, ROGERS PAW (1992) Progesterone and oestrogen receptor distribution in endometrium from "Norplant" users. Proc. Endocrine Soc. Aust., Adelaide, September 27-30th, p114.

85. LEETON J, CALDERON I, AZUMA K, KING C, BURDEN J, ROGERS P (1992) The main factor in infertility: Egg or endometrium? The American Fertility Society, 48th Annual Meeting, New Orleans, USA. 2-5th November, P-042.

86. LEETON J, CALDERON I, AZUMA K, BURDEN J, RENOU P, KING C, ROGERS P (1992) Pregnancy outcome of 50 women treated successfully on a donor oocyte program. The American Fertility Society, 48th Annual Meeting, New Orleans, USA. 2-5th November, P-146.

87. WONODIREKSO S, AU CL, ROGERS PAW (1992) Cytokeratin 8, 18 and 19 in endometrial epithelial cells during the normal menstrual cycle and in women receiving Norplant. Fertility Society of Australia, 11th Annual Conference, Adelaide, South Australia. December 2-5th.

88. ABBERTON KM, AU CL, TAYLOR N, SUSIL B, ROGERS PAW (1992) Endometrial microvascular Factor VIII related antigen in women with and without increased perimenopausal bleeding. Fertility Society of Australia, 11th Annual Conference, Adelaide, South Australia. December 2-5th.

89. MCCLURE N, ABBERTON K, HEALY DL, MACPHERSON A, ROGERS PAW (1992) Follicular fluid maturity and endothelial cell mitogenesis. Fertility Society of Australia, 11th Annual Conference, Adelaide, South Australia. December 2-5th.

90. CRITCHLEY HOD, BAILEY DA, HEALY DL, ROGERS PAW (1992) Sex steroid receptor distribution in endometrium from women with menorrhagia before and after endometrial ablation. Fertility Society of Australia, 11th Annual Conference, Adelaide, South Australia. December 2-5th.

91. MACPHERSON AM, ROGERS PAW (1992) Proliferating endothelial cells in the rat uterus prior to embryo implantation. 2nd Baker Institute Symposium, Melbourne, 11-13th December.

92. ROGERS PAW (1992) Endometrial angiogenesis. 2nd Baker Institute Symposium, Melbourne, 11-13th December.

93. ROGERS PAW, AU CL, AFFANDI B (1992) Endometrial microvascular density following exposure to long-term progestogen contraception. Proceedings of the 31st National Scientific Conference, Australian Society for Medical Research, Brisbane, 13-16th December.

94. CRITCHLEY HOD, AU CL, BAILEY DA, AFFANDI B, ROGERS PAW (1992) Progesterone and oestrogen receptor distribution in endometrium from "Norplant" users. Proceedings of the 31st National Scientific Conference, Australian Society for Medical Research, Brisbane, 13-16th December.

95. ARCHBOLD DC, ROGERS PAW (1992) Expression of LFA-1, MAC-1 and LCA in human endometrium throughout the normal menstrual cycle. Proceedings of the 31st National Scientific Conference, Australian Society for Medical Research, Brisbane, 13-16th December.

96. MARSH MM, BUTT AR, ROGERS PAW, SALAMONSEN LA, FINDLAY JK (1992) Immunolocalization of endothelin in the endometrium of Norplant users. Proceedings of the 31st National Scientific Conference, Australian Society for Medical Research, Brisbane, 13-16th December.

97. MACPHERSON AM, ROGERS PAW (1993) Proliferating endothelial cells in the human endometrium during the menstrual cycle. Prog. Microcirc. Res., Proc. 7th Aust. NZ Symposium, 7-9 Feb, pp24-26.

98. WINGFIELD M, MACPHERSON A, HEALY DL, ROGERS PAW (1993) Endothelial cell proliferation in endometriosis. Prog. Microcirc. Res., Proc. 7th Aust. NZ Symposium, 7-9 Feb, pp28-30.

99. ROGERS PAW, AU CL, CRITCHLEY HOD, AFFANDI B (1993) Basic studies on endometrial bleeding in norplant users. Proc. VIIIth World Congress on Human Reproduction, Bali, Indonesia. April 4-9th. pp97.

100. TAWIA SA, BEATON LA, ROGERS PAW (1993) Immunolocalization of cellular adhesion molecules in human endometrium throughout the menstrual cycle. Presented at: Genes and Development; A Scientific Meeting to Open the Monash University Institute of Reproduction and Development. Abstract No. 8.

101. MACPHERSON AM, ROGERS PAW (1993) Human endometrial endothelial cell proliferation during the menstrual cycle. Australian Society for Reproductive Biology, Proceedings 25th Annual Conference. Dunedin, NZ August 23-25th, pp 79.

102. ABBERTON KM, ROGERS PAW TAYLOR N, CRITCHLEY HOD (1993) Endometrial oestrogen and progesterone receptor expression in women with menorrhagia. Australian Society for Reproductive Biology, Proceedings 25th Annual Conference. Dunedin, NZ August 23-25th, pp 81.

103. ROGERS PAW, MACPHERSON AM, ABBERTON KM (1993) Endometrial angiogenesis during the menstrual cycle. Symposium on: "New cancer strategies: Angiogenesis and angiogenesis antagonists". Philadelphia, USA, October 18-19.

104. AU C.L, ROGERS PAW, AFFANDI B (1993) Endometrial vascular density and endothelial cell von Willebrand factor levels in Norplant users. Hong Kong Society for the Study of Endocrinology Metabolism & Reproduction 8th Annual Scientific Meeting. October 30th.

105. CRITCHLEY HOD, SUSIL B, KOOY J, HEALY DL, ROGERS PAW (1993) Endometrial morphology following endometrial ablation. The Fertility Society of Australia XII Annual Scientific Meeting in conjunction with the Australian Gynaecological Endoscopy Society III Annual Scientific Meeting. Sydney, November 2-6th. Abstract No. 06.

106. WINGFIELD M, MACPHERSON A, HEALY DL, ROGERS PAW. (1993) Endothelial cell proliferation in endometriosis. The Fertility Society of Australia XII Annual Scientific Meeting in conjunction with the Australian Gynaecological Endoscopy Society III Annual Scientific Meeting. Sydney, November 2-6th. Abstract No. 0109.

107. ROGERS PAW, AFFANDI B. (1993) Research on progestogen-induced vaginal bleeding: a collaboration between Indonesia and Australia. 14th Asian and Oceanic Congress of Obstetrics and Gynaecology, Manila, November 14-19th.

108. AREVALO J, HEALY D, CRITCHLEY H, ROGERS PAW. (1993) The role of macrophages in the endometrium. Thirty-Second National Scientific Conference. The Australian Society for Medical Research. Adelaide, November 28th-December 1st. Abstract No. 010.

109. LEDERMAN FL, ROGERS PAW. (1993) Endometrial Angiogenesis: Production of endothelial cell migratory factor. Thirty-Second National Scientific Conference. The Australian Society for Medical Research. Adelaide, November 28th-December 1st. Abstract No. 014.

110. KELLY FD, TAWIA SA, RICE GE, ROGERS PAW. (1993) Microvascular heterogeneity in human endometrium. Thirty-Second National Scientific Conference. The Australian Society for Medical Research. Adelaide, November 28th-December 1st. P-9.

111. KOOY J, CRITCHLEY HOD, HEALY DL, ROGERS PAW. (1993) Vascular growth in post-ablation human endometrium. Thirty-Second National Scientific Conference. The Australian Society for Medical Research. Adelaide, November 28th-December 1st. P-10.

112. JAMES JM, ROGERS PAW. (1994) The "mysterious" calcite precipitating organism of the Nullarbor caves, Australia. Breakthroughs in Karst Geomicrobiology and Redox Geochemistry. Colorado Springs, USA, February 16-19th.

113. WINGFIELD M, MACPHERSON A, HEALY DL, ROGERS PAW. (1994) Endothelial Cell Proliferation in Endometriosis. IVth World Congress on Endometriosis, Salvador, Bahia, Brazil. May 25-28th.

114. KOOY J, TAYLOR NH, HEALY DL, ROGERS PAW. (1994) Endothelial cell proliferation in the endometrium of menorrhagic and post-ablation subjects. Fertility Society of Australia, XIII Annual Scientific Meeting, Brisbane, October 3-7th.

115. ABBERTON KM, TAYLOR NH, ROGERS PAW. (1994) Differences in the endometrial microvasculature of women with or without perimenopausal menorrhagia. Fertility Society of Australia, XIII Annual Scientific Meeting, Brisbane, October 3-7th.

116. LAU TM, AFFANDI B, ROGERS PAW. (1994) Expression of cathepsin D in control and levonorgestral exposed human endometrium. Australian Society for Medical Research, Thirty-Third National Scientific Conference, Melbourne, November 27-30th.

117. LOTFI-MIRI M, ROGERS PAW, MAMERS P, SUSIL B, QUINN M. (1994) Endothelial cell proliferation in malignant and benign human ovarian tumours. Australian Society for Medical Research, Thirty-Third National Scientific Conference, Melbourne, November 27-30th .

118. PALMER JA, LAU T, ROGERS PAW. (1994) The basement membrane in the endometrial microvasculature of Norplant users. Australian Society for Medical Research, Thirty-Third National Scientific Conference, Melbourne, November 27-30th.

119. TAWIA SA, ROGERS PAW. (1994) Immunohistochemical localisation of vascular basement membrane components during rat embryo implantation. Australian Society for Medical Research, Thirty-Third National Scientific Conference, Melbourne, November 27-30th.

120. MARSH MM, BUTT AR, ROGERS PAW, FINDLAY JK, SALAMONSEN LA. (1994) Relationship between menstrual bleeding and endothelin immunolocalized in the endometrium of users of subdermally implanted levonorgestrel. Aust Soc Med Res, Thirty-Third National Scientific Conference, Melbourne, November 27-30th.

121. ROGERS PAW. (1995) Reproductive angiogenesis. Progress in Microcirculation Research. Proceedings of the Eighth Australian and New Zealand Symposium. February 2-4th.

122. HADISAPUTRA W, WITJAKSONO J, AFFANDI B, ROGERS PAW. (1995) Endometrial biopsy collection. WHO sponsored meeting on "Current Research on Progestin-only Contraceptives and Endometrial Bleeding". Bali, October 14-15th.

123. ROGERS PAW. (1995) The endometrial vasculature. WHO sponsored meeting on "Current Research on Progestin-only Contraceptives and Endometrial Bleeding". Bali, October 14-15th.

124. LAU TM, AFFANDI B, ROGERS PAW. (1995) In situ hybridisation studies on endometrial progesterone receptor in Norplant users and during the normal cycle. WHO sponsored meeting on "Current Research on Progestin-only Contraceptives and Endometrial Bleeding". Bali, October 14-15th.

125. WITJAKSONO J, LAU T, ROGERS PAW. (1995) Effects of estrogen treatment on the endometrium of Norplant users. WHO sponsored meeting on "Current Research on Progestin-only Contraceptives and Endometrial Bleeding". Bali, October 14-15th.

126. WONODIREKSO S, ROGERS PAW. (1995) Endometrial cytokeratins in users of Norplant and norethisterone enanthate (NET-EN). WHO sponsored meeting on "Current Research on Progestin-only Contraceptives and Endometrial Bleeding". Bali, October 14-15th.

127. PALMER JA, LAU TM, HICKEY M, ROGERS PAW. (1995) Immunohistochemical study of endometrial microvascular basement membrane components in women using Norplant. Fertility Society of Australia, Melbourne, November 19-25th. FSA 71.

128. ABBERTON KM, TAYLOR N, ROGERS PAW. (1995) Endometrial vascular smooth muscle cell proliferation in women with or without menorrhagia. Fertility Society of Australia, Melbourne, November 19-25th. FSA 73.

129. ROGERS PAW, LEDERMAN F, KOOY J, TAYLOR N, HEALY DL. (1995) Endometrial vascular smooth muscle oestrogen and progesterone receptor distribution in women with and without menorrhagia. Fertility Society of Australia, Melbourne, November 19-25th. FSA 74.

130. TAYLOR NH, ROGERS PAW, HEALY DL. (1995) Clinical evaluation of endometrial ablation for menorrhagia. Fertility Society of Australia, Melbourne, November 19-25th. FSA 148.

131. WITJAKSONO J, LAU TM, HEALY DL, ROGERS PAW. (1995) Estrogen treatment for increased bleeding in Norplant users. Fertility Society of Australia, Melbourne, November 19-25th. FSA 149.

132. ABBERTON KM, HEALY DL, ROGERS PAW. (1996) Vascular smooth muscle cell proliferation in the human endometrium. Sixth World Congress for Microcirculation, Munich, Germany, August 25-30th. P480.

133. ROGERS PAW, LEDERMAN F, KOOY J, TAYLOR N, HEALY DL. (1996) Endometrial vascular smooth muscle oestrogen and progesterone receptor distribution in women with and without menorrhagia. Sixth World Congress for Microcirculation, Munich, Germany, August 25-30th. P481.

134. HII LL, ROGERS PAW. (1996) Expression of integrin ?v?3 in human endometrium throughout the menstrual cycle. 4th Annual Scientific Meeting, Marysville, Victoria, October 17-20. 15.

135. WINGFIELD M, MACPHERSON A, ROGERS PAW, HEALY DL. (1996) Endometrium in endometriosis. Vth World Congress on Endometriosis, Yokohama, Japan, October 21-24. 0-63.

136. WINGFIELD M, MACPHERSON A, ROGERS PAW, HEALY DL. (1996) Endometrial CA125 in endometriosis. Vth World Congress on Endometriosis, Yokohama, Japan, October 21-24. P-87.

137. LEDERMAN FL, TAYLOR NH, ROGERS PAW. (1996) Regional variability in endometrial endothelial cell proliferation within the uterus. The Australian Society for Medical Research. 35th National Scientific Conference, Gold Coast, Queensland. November 24-27th. POS-1-10.

138. ORRE M, MAMERS P, SUSIL B, QUINN M, HEALY DL, ROGERS PAW. (1996) Vascular endothelial growth factor and microvessel density in tumours of the ovary. The Australian Society for Medical Research. 35th National Scientific Conference, Gold Coast, Queensland, November 24-27th. POS-2-17.

139. LEDERMAN FL, TAYLOR NH, ROGERS PAW. (1997) Regional variability in endometrial endothelial cell proliferation within the uterus. Australian and New Zealand Microcirculation Society. Ninth Microcirculation Symposium. Melbourne, Victoria, January 31 - February 2.

140. ORRE M, ROGERS PAW (1997) Vascular and non-vascular cell proliferation in tumours of the ovary. Australian and New Zealand Microcirculation Society. Ninth Microcirculation Symposium. Melbourne, Victoria, January 31 - February 2.

141. ABBERTON KM, HEALY DL, ROGERS PAW (1997) Vascular smooth muscle cell proliferation in the arterioles of human endometrium. Australian and New Zealand Microcirculation Society. Ninth Microcirculation Symposium. Melbourne, Victoria, January 31 - February 2.

142. LOFTI-MIRI M, ROGERS PAW (1997) Vascularisation of the ovarian follicle prior to ovulation in the rat. Australian and New Zealand Microcirculation Society. Ninth Microcirculation Symposium. Melbourne, Victoria, January 31 - February 2.

143. ROGERS PAW (1997) Endometrial microvascular growth in normal and dysfuncational states. International Ferring Symposium on Function and Dysfunction of the Non-pregnant Uterus. Germany, June 19-21.

144. ROGERS PAW (1997) Endometrial angiogenesis. Gordon Research Conference, Boston, USA, 19-22 August.

145. ROSAMILIA A, CANN L, DWYER PL, ROGERS PAW (1997) Bladder microvasculature in women with interstitial cystitis. International Continence Society. Japan, 23-26

September.

146. VINCENT AJ, MALAKOOTI N, AFFANDI B, ROGERS PAW, SALAMONSEN LA. (1997) Matrix metalloproteinase-9 and migratory cells and associated with abnormal uterine bleeding in women. Australian Society for Reproductive Biology. Canberra, ACT, 29 September - 1 October.

147. ROSAMILIA A, CANN L, DWYER PL, ROGERS PAW (1997) Bladder microvasculature in interstitial cystitis. International Research Symposium on Interstitial Cystitis. Washington, D.C., October 30-31.

148. ORRE M. ROGERS PAW (1997) Vascular differences between mucinous and serous ovarian tumours. Second Peter Mac Symposium. New Strategies for Cancer Detection and Therapy. Melbourne, Victoria, November 9-12.

149. ABBERTON K, ROGERS PAW (1997) Transforming growth factor and endothelin in the endometrium of women with menorrhagia. The Australian Society for Medical Research. 36th National Scientific Conference. Adelaide, S.A. 23-26 November 1997.

150. LAU TM, AFFANDI B, ROGERS PAW (1997) VEGF expression in normal and Norplant endometrium. The Australian Society for Medical Research. 36th National Scientific Conference. Adelaide, S.A. 23-26 November 1997.

151. WEBSTER D, ROGERS PAW, LEETON J. (1997) Monash IVF donor oocyte program - Data 1993-1996. The Fertility Society of Australia. XVI Annual Scientific Meeting. Adelaide, 2-4 December 1997.

152. LEDERMAN F, TADOKORO N, ROGERS PAW. (1997) Correlation of vascular endothelial growth factor (VEGF) expression with endothelial cell proliferation in the rat uterus during early pregnancy. The Fertility Society of Australia. XVI Annual Scientific Meeting. Adelaide, 2-4 December 1997.

153. VOLLENHOVEN B, BAKKER M, TAYLOR N, LAWRENCE M, ROGERS PAW. (1997) Representational difference analysis: a new and valuable tool for studying the aetiology of fibroids. The Fertility Society of Australia. XVI Annual Scientific Meeting. Adelaide, 2-4 December 1997.

154. LEETON J, STEPHENS S, WITHERS R, WEBSTER D, ELDAR-GEVA T, ROGERS PAW. (1997) Clinical factors determining pregnancy rate on a donor egg program. The Fertility Society of Australia. XVI Annual Scientific Meeting. Adelaide, 2-4 December 1997.

155. ROGERS PAW, GARGETT C, LEDERMAN F, TAYLOR N, LAU T. (1998) VEGF production by cultured human endometrial tissue and separated cells. Keystone Symposium on Molecular and Cellular Biology. Angiogenesis and Vascular Remodelling. Steamboat Springs, Colorado, March 28 - April 3, 1998.

156. VOLLENHOVEN B, ROGERS PAW, HEALY DL. Uterine fibroids, what makes them grow? Victorian Women's Health Conference, Melbourne, June 9-10, 1998.

157. ROGERS PAW, GARGETT C, LEDERMAN F, TAYLOR N, LAU T, WINGFIELD M, HEALY DL. Endometrial angiogenesis. VI World Congress on Endometriosis. Quebec, Canada, June 30-July 4, 1998.

158. VOLLENHOVEN BJ, BAKKER M, TAYLOR N, LAWRENCE M, ROGERS PAW. (1998) Are there unique genes in uterine leiomyomas compared with normal myometrium which would explain the growth of these tumours? American Society for Reproductive Medicine. 54th Annual Meeting. USA, October 3-9, 1998.

159. ROGERS PAW, GARGETT C, LEDERMAN F, TAYLOR N, LAU T (1998) Lack of correlation between VEGF production and angiogenesis in human endometrium. Fertility Society of Australia Hobart, October 28 - November 1, 1998.

160. HEFFERNAN C, GARGETT CE, ROGERS PAW (1998) Angiogenesis inhibitors in human endometrium. Australian Society for Medical Research 37th National Scientific Conference. Hobart, November 22-25, 1998.

161. BUCAK K, GARGETT CE, ROGERS PAW (1998) Isolation and culture of human myometrical microvascular endothelial cells. Australian Society for Medical Research 37th National Scientific Conference. Hobart, November 22-25, 1998.

162. VINCENT AL, MALAKOOTI N, ROGERS PAW, AFFANDI B, SALAMONSEN LA (1998) Endometrial breakdown in women using Norplant is associated with migratory cell expression of matrix metallopreinase-9 (gelatinaseB). Soc Syn Invest

163. ROGERS PAW, GARGETT C, HEFFERNAN C, LEDERMAN F, TAYLOR N (1999) Regulation of angiogenesis in human endometrium: The role of angiogenesis promoters and inhibitors. Proceedings of the Tenth Australian and New Zealand Microcirculation Symposium, Adelaide 27-29 January 1999.

164. GARGETT CE, BUCAK K, ROGERS PAW (1999) Isolation and characterisation of human myometrial microvascular endothelial cells. Proceedings of the Tenth Australian and New Zealand Microcirculation Symposium, Adelaide 27-29 January 1999.

165. ABBERTON KM, ROGERS PAW (1999) Expression of the receptor tyrosine kinases tie-1 and tie-2 in the microvasculature of the human uterus. Proceedings of the Tenth Australian and New Zealand Microcirculation Symposium, Adelaide 27-29 January 1999.

166. ROGERS PAW, ORRE M. (1999) Angiogenesis in ovarian cancer. Institute of Reproduction and Development Symposium. Victoria May 7-8, 1999.

167. VOLLENHOVEN BJ, CASEY R, ROGERS PAW (1999) An immunohistochemical analysis of fibroid vasculature. American Society of Reproductive Medicine, Toronto,

Canada, 25-30 September 1999.

168. GARGETT C, LEDERMAN F (1999) Focal VEGF correlates with angiogenesis in human endometrium. The Australian Society for Medical Research, NSW, 27 - 29 November 1999.

169. ZAITSEVA M, ROGERS P, GARGETT C. (1999) Estrogen regulation of VEGF receptors in human myometrium and fibroids. The Australian Society for Medical Research, NSW, 27 - 29 November 1999.

AUSTRALIA

Patents Act 1990

IN THE MATTER OF Australian Patent Application Serial No 696764 by Human Genome Sciences, Inc.

-and-

IN THE MATTER OF Opposition thereto by Ludwig Institute for Cancer Research

STATUTORY DECLARATION

I, Kari Alitalo of The Molecular/Cancer Biology Laboratory, Haartman Institute, University of Helsinki, SF-00014 Helsinki, Finland do solemnly and sincerely declare as follows :

Introduction

1. Background

I am presently working as Research Professor with The Finnish Medical Research Council of the Finnish Academy of Sciences. Since receiving my M.D. and M.Sc.D. in 1977 and 1980, respectively, from the University of Helsinki, I have worked substantially continuously as a professor and scientific researcher in Finland in areas of cellular and molecular biology and cancer research. My research has included substantial studies and explorations in fields of cancer, cancer metastasis, angiogenesis, lymphangiogenesis, and other areas related to angiogenesis. In addition to my own research efforts and my collaborations with others, I receive numerous invitations to speak at national and international symposiums in these areas of study, I supervise post-graduate research of others, I have authored and co-authored numerous original research articles published in peer-reviewed journals, and I have served on the editorial board of such journals. My detailed *curriculum vitae* is attached hereto as Exhibit 1.

1.2 I have conducted and collaborated in substantial research relating to a growth factor gene and protein that my laboratory calls "Vascular Endothelial Growth Factor C" or "VEGF-C." My attached *curriculum vitae* shows that I have co-authored several publications in peer-reviewed journals relating to the VEGF-C gene and protein, its synthesis and processing in cells, and its biological activities *in vitro* and *in vivo*. Among these publications are the following:

Document D70: Joukov et al., "A Novel Vascular Endothelial Growth Factor, VEGF-C, Is a Ligand for the Flt4 (VEGFR-3) and KDR (VEGFR-2) Receptor Tyrosine Kinases," *EMBO J., 15(2)*: 290-298 (1996).

Document D71: Joukov et al., "Proteolytic Processing regulates receptor specificity and activity of VEGF-C," EMBO J., 16(13): 3898-3911 (1997)

Document D74: Kukk et al., "VEGF-C receptor binding and pattern of expression with VEGFR-3 suggests a role in lymphatic vascular development," *Development, 122*: 3829-37 (1996).

I also have filed patent applications relating to VEGF-C, VEGF-C variants, and uses thereof. Among these applications are the following applications:

Document D72: International Patent Application No. PCT/FI96/00427, filed on 1 August 1996 by Helsinki University Licensing Ltd Oy (WO 97/05250).

Document D73: International Patent Application No. PCT/US98/01973, filed on 2 February 1998 by Ludwig Institute for Cancer Research et al. (WO 98/33917).

Thus, my laboratory and my collaborators have substantial expertise and experience working with and expressing the VEGF-C gene and protein.

1.3 I am familiar with the opposition filed by Ludwig Institute for Cancer Research ("Ludwig Institute") to the issuance of a patent to Human Genome Sciences, Inc., ("HGS") based on HGS's Australian Patent Application No. 696764 ("the opposed application"). Ludwig Institute asked me to perform a protein expression study that may be relevant to the opposition, and provide this declaration in which I report the study and the results.

1.4 In making this declaration to the Australian Patent Office, I understand that I have an overriding duty to the Patent Office (and to any Australian Federal Court that should review the Patent Office decision) to provide objective scientific analysis that I believe to be truthful. I hereby affirm that, to the best of my knowledge and belief, factual statements herein are true and opinion statements herein represent my objective scientific opinion and analysis.

II. VEGF2 and VEGF-C

2.1 The human growth factor which my laboratory and others in the scientific community call "VEGF-C" is encoded by a human gene having 419 codons. The coding sequence of a VEGF-C cDNA may be found in **Document D73** or in the publicly accessible Genbank database under Accession No. X94216.

2.2 The 350 amino acid VEGF-2 polypeptide sequence disclosed in the opposed application of Human Genome Sciences, entitled "Vascular Endothelial Growth Factor 2" (VEGF-2(HGS)) corresponds to amino acid residues 70 to 419 of human VEGF-C (Genbank Accession No. X94216), with the exception of a single amino acid difference (Lys/Gln) at position 414 of the VEGF-C sequence.[1] HGS subsequently filed a later patent application that contained a 419 amino acid "full length" VEGF2 sequence. (See, e.g., Fig 1A-1E of **Document D44** (WO 96/39515)) The 419 residue VEGF-C and VEGF2 sequences are identical except for two amino acid differences: one at position 3 (Leu/Ser), and another at position 414 (Lys/Gln) of the VEGF-C sequence. Thus, my experience working with VEGF-C is applicable to working with VEGF2.

III. Signal Peptides

[1] The opposed patent application actually contains sequence ambiguities. If one compares the VEGF-C sequence with the VEGF2 sequence in the Sequence Listing of the opposed application, one observes amino acid differences at residue 73 and 414, and an insertion of an extra Cys residue in the VEGF2 sequence at a location between residues 369 and 370 of the 419 residue VEGF-C sequence. Based on HGS's later filed patent applications, I have concluded that the VEGF2 sequences in the figures were more appropriate to use in the experiments described herein.

3.1 Polypeptides such as growth factors that are destined for extracellular secretion are first synthesized in the cellular cytoplasm. Such polypeptides generally include a short secretory signal peptide at their amino terminus that is usually cleaved off, but serves as a vital signal to direct the nascent polypeptide into the cell's protein secretion apparatus.

3.2 Scientific experiments in my laboratory has determined that the first approximately 31 amino acids from the 419 amino acid form of VEGF-C serve as a signal peptide. The experimental details and evidence underlying this determination are reported in **Document D71.**

3.3 In the opposed patent application, the 350 amino acid VEGF2 sequence is lacking the 31 amino acids that represent the VEGF-C signal peptide. In the application, the inventors assert that the first 24 amino acids of their VEGF2 sequence (which would approximately correspond to amino acids 70-93 of the full-length 419 amino acid VEGF-C sequence) operate as a signal peptide.

Experimental Purpose

4.1 In view of my laboratory's expertise in expressing and working with the VEGF-C gene and protein, the Ludwig Institute asked me to perform experiments to determine whether or not the 350 amino acid protein contains an operative signal peptide, as alleged in the opposed application.

Experimental Design

I. Overview

5.1 The accumulated knowledge of molecular biologists regarding signal peptides have permitted biologists to identify certain characteristic features of signal peptides. (One such feature is an amino acid composition comprising largely hydrophobic residues.) Computer programs have been designed to predict whether an amino acid sequence begins with a signal peptide, and to identify the site in an amino acid sequence where a putative signal peptide is cleaved. As a first part of my analysis, I used one such

program, the SignalP program at the Center for Biological Sequence Analysis, The Technical University of Denmark, to analyze the approximately 350 amino acid VEGF2 sequence for a series of residues having characteristics of a signal sequence.

5.2. As a second part of my analysis, I transformed a mammalian cell line with an expression vector containing a polynucleotide that encodes the 350 amino acid VEGF2 sequence ("VEGF2(HGS)"), grew the cell line under conditions in which the cells produce polypeptides, and then assayed the growth medium of the cells to determine whether the cells were secreting VEGF2. These experiments included various experimental controls to assure that there was no problem with the expression vector, the cells, the transformation procedures, the growth conditions, or other parameters. The actual details of the experimental protocol are described in the next section.

II. Detailed Experimental Protocol

6.1 To determine whether eukcaryotic cells can express and secrete VEGF2(HGS), an expression plasmid containing a VEGF2(HGS) polynucleotide sequence was constructed. This involved preparing a VEGF2(HGS) DNA fragment, and inserting the fragment into a commercial expression vector.

6.1.1 The polymerase chain reaction (PCR) was employed to construct a DNA fragment that encodes amino acids 70 to 419 of VEGF-C, followed by a short hemagglutinin (HA) tag fused in-frame to the 3' end of the VEGF-C coding region.[2] The 5'-primer used in the PCR reaction contained a BamHI restriction endonuclease recognition site followed by the first 18 nucleotides from the VEGF-C(70-419) coding sequence. The 3'-primer contained an XbaI recognition

[2] As explained above, amino acids 70-419 of VEGF-C differ at position 414 from the VEGF2(HGS) amino acid sequence presented in the figures of the opposed patent. Since any signal peptide in VEGF2(HGS) would occur at the *beginning* (amino terminus) of the VEGF2(HGS) sequence, a single change at position 414, and the inclusion of a HA-tag at the end (carboxy terminus) are inconsequential to this expression study. These assumptions are verified by the VEGF-C positive control that was included in these experiments, and by the ability of my laboratory and many other laboratories to recombinantly express other polypeptides with a carboxy terminal HA tag to facilitate purification.

site, an HA-tag, a stop codon, and the last 15 nucleotides from the VEGF-C(70-419) coding region, excluding the stop codon. The locations of the 5' and 3' primers with respect to the complete VEGF-C cDNAsequence (which was used as PCR template DNA), are shown in Exhibit 2 attached hereto.

6.1.2 The resulting PCR product was digested with BamHI and XbaI and inserted into the multiple cloning site of the commercially available expression vector pcDNA1/Amp (Invitrogen) that had been digested with the same enzymes. This construct was named VEGF2(HGS)/pcDNA1, and DNA sequencing was performed to confirm that the VEGF2(HGS) insert was present and in the correct orientation for expression.

6.1.3 To serve as an experimental control, a similar expression plasmid, designated VEGF-C/pcDNA1 was also constructed. In this expression plasmid, a DNA encoding the complete 419 amino acid VEGF-C polypeptide was cloned into pcDNA1.

6.2 The 293T mammalian cell line was selected for the expression study. Thus, 293T cells, grown in DMEM medium supplemented with 10% fetal bovine serum, glutamine and penicillin/streptomycin, were mock-transfected (control), transiently transfected with VEGF2(HGS)/pcDNA1, or transiently transfected with VEGF-C/pcDNA1 using the calcium-phosphate method.

6.3 Radioactive amino acids that would be incorporated into nascent polypeptides were introduced into the cell growth medium to assist in the identification of expressed polypeptides. In particular, 48 hours after transfection, the transfected cells were washed twice with phosphate-buffered saline (PBS) and metabolically labeled in MEM medium containing 100μCi/ml ^{35}S-methonine and ^{35}S-cysteine (Promix, Amersham) for 6 hours. The conditioned media was harvested and cleared of contaminants by centrifugation. After washing three times with ice cold PBS, the cells were lysed in ice cold RIPA-buffer

(150 mM NaCl, 1% NP-40, 0.5% DOC, 0.1% SDS, 50 mM Tris); supplemented with 0.01 U/ml aprotinin, 1μg/ml leupeptin, and 1mM PMSF; and the lysate was cleared by centrifugation.

6.4 Before analysis for expressed VEGF2(HGS) and VEGF-C, steps were taken to assure that any low levels of VEGF produced by 293T cells would not confound the results. Endogenous VEGF was removed from the conditioned media and cell lysates by incubation with 1 μg/ml monoclonal anti-human VEGF antibody (R & D Systems), followed by precipitation of the immunocomplexes with protein A-Sepharose (Amersham Pharmacia Biotech).

6.5 Next, an immunoprecipitation was conducted to capture any VEGF2(HGS) or VEGF-C from the conditioned media or cell lysates. For immunoprecipitation, the conditioned media was supplemented with BSA, Tween 20, and heparin to final concentrations of 0.5%, 0.02%, and 1 μg/ml, respectively. VEGF2(HGS) was immunoprecipitated at 4 C with 4 μg/ml monoclonal anti-HA antibody (HA.11, BabCO), and VEGF-C was immunoprecipitated at 4 C with 882 antiserum, a polyclonal antibody raised against a synthetic peptide corresponding to residues 35-51 of the 350 amino acid VEGF2 polypeptide. The immunocomplexes were collected on protein A-Sepharose and washed twice with 1X binding buffer (0.5% BSA, 0.02% Tween 20, 1 μg/ml heparin), and once with 20 mM TrisHCl pH 7.4 at 4 C. The proteins were analyzed on 15% SDS-PAGE under reducing conditions.

Experimental Results

7.1 Analysis of the VEGF2(HGS) sequence with the SignalP program indicated that this 350 amino acid sequence does not begin with a sequence having hydrophobicity characteristics of a signal sequence.

7.2 An autoradiogram of the SDS-PAGE gel is attached hereto as Exhibit 3. That exhibit shows that the VEGF2(HGS) polypeptide is detected in cell lysates (lane 4), but not

conditioned media (lane 1), from 293T cells transfected with VEGF2(HGS)/pcDNA1. In contrast, VEGF-C polypeptide was detected in both cell lysates (lane 5) and conditioned media (lane 2) from 293T cells transfected with VEGF-C/pcDNA1. VEGF2(HGS) detected in cell lysates migrates as a circa 46 kD protein, whereas the majority of VEGF-C detected in the conditioned media migrated as a broad doublet band of approximately 29-31 kD polypeptides and another band of about 21 kD. A significant quantity of higher molecular weight polypeptides were observed in the cell lysates of the VEGF-C-transfected cells, which I interpret as VEGF-C "captured" at various stages of proteolytic processing[3] (as a result of lysing the cells six hours after labeling. In addition, it is readily apparent from the autoradiogram that the expression level of VEGF-C is much higher than that of VEGF2(HGS).

Analysis

8.1 If VEGF2(HGS)-transfected cells had secreted any VEGF2(HGS) protein, the protein would have been captured by the anti-HA antibody and visualized in the conditioned medium from these cells (Exhibit 3, lane 1). No VEGF2(HGS) was observed in this lane, indicating that no VEGF2(HGS) secretion was occurring. Thus, I conclude that the 350 amino acid VEGF2 sequence taught in the opposed application does NOT contain a signal peptide sequence. This conclusion is further supported by the computer analysis which failed to identify any sequence in the 350 residue VEGF2 that has hydrophobicity characteristics of a signal peptide.

8.2 The experimental procedures were sound, as evinced by the high level of secreted VEGF-C that was observed in the conditioned media of cells that had been transfected with the full-length VEGF-C cDNA construct (lane 2), and the observation of a well-defined, unsecreted 46 kD polypeptide band captured by the anti-HA antibody from the cell lysate of VEGF2(HGS)-transfected cells.

[3] A detailed description of VEGF-C proteolytic processing is set forth in Document D71, which I incorporate herein by reference.

8.3 The fact that VEGF-C expression observable in cell lysates of VEGF-C-transfected cells is much higher than VEGF2(HGS) expression observable in VEGF2(HGS)-transfected cells suggests that VEGF2(HGS) is inefficiently translated and/or that the intracellular turnover rate of VEGF2(HGS) is much faster than that of VEGF-C. In other words, the cells may be recognizing VEGF2(HGS) as an aberrant protein and rapidly degrading it.

Summary

9.1 The failure of cells transfected with an expression vector containing the 350 amino acid VEGF2 cDNA sequence taught in the opposed patent application to secrete any VEGF2 protein indicates that the 350 amino acid VEGF2 cDNA sequence taught in the opposed application does not contain a functional signal peptide, as the patent applicants allege.

AND I MAKE this solemn declaration by virtue of the Statutory Declarations Act 1959, and subject to the penalties provided by that Act for the making of false statements in statutory declarations, conscientiously believing the statements contained in this declaration to be true in ev · particular.

DECLARED at Helsinki

this 15th day of February 2000

Kari Alitalo

BEFORE ME:

OLLI-PEKKA SIRO
Notary Public
Notary Public

AUSTRALIA

Patents Act 1990

IN THE MATTER OF Australian Patent Application Serial No 696764 by Human Genome Sciences, Inc.

-and-

IN THE MATTER OF Opposition thereto by Ludwig Institute for Cancer Research

THIS IS Exhibit 1 referred to in the Statutory Declaration of Kari Alitalo made before me this 15th Day of February, 2000

OLLI-PEKKA SIRO
Notary Public

HELSINGIN MAISTRAATTI
MAGISTRATEN I HELSINGFORS

CURRICULUM VITAE

Kari Kustaa Alitalo, born 21.05.52

Position:

Research Professor, the Finnish Medical Research Council of the Finnish Academy of Sciences
1.8.1993-31.7.2003

Education:

Educational Commission for Foreign Medical Graduates (USA) - exam	1976
M.D. University of Helsinki	1977
M.Sc.D. (basic sciences, corresponding to Ph.D. degree) University of Helsinki	1980

Previous professional appointments:

Research and teaching assistantships, Departments of Pathology, Virology, State Medical Research Council, The Finnish Academy of Sciences	1977-1982
Visiting Scientist, Department of Biochemistry, University of Washington, Seattle, USA (Dr. Paul Bornstein)	1981-1982
Visiting Scientist, Department of Microbiology and Immunology, University of California, San Francisco, USA (Dr. J. Michael Bishop and Dr. Harold E. Varmus)	1982-1983
Research Fellow, Senior RF, State Medical Research Council	1983-1986
Professor of Medical Biochemistry, University of Turku	12.1986-10.1987
Research Professor, The Finnish Cancer Institute	10.1987-07.1988
Professor of Cancer Biology, University of Helsinki	07.1988-07.1993
Professor of Medical Biochemistry, University of Helsinki	10.1996-
Research Professor, the Finnish Academy of Sciences	08.1993-

Research awards and honours:

Primus Doctorum in the X Promotion of The Medical Faculty, University of Helsinki	1981
The Jahre Prize, Oslo, Norway	1987
Farmos Oy: Science Prize, Turku, Finland	1987
The Medix Prize for the Best Finnish Paper in the Biosciences in 1989	1990
The Finnish Medical Society Duodecim Äyräpää Prize	1998
The Medix Prize for the Best Finnish Paper in the Biosciences in 1997	1998
Europe Medecine Senior Prize	1999

Editorial board memberships:

EMBO Journal	1994-1998 2000-
The FASEB Journal	
International Journal of Cancer	
British Journal of Cancer	

Memberships in scientific societies:

European Molecular Biology Organization	1990-
Fund Committee	1994-1997

The Scientific Council, IARC/WHO	1991-1995
Nordic.Molecular Biology Association (NOMBA)	1995-
Executive board	1990-1992
Scientific Evaluation group, International Cancer Technology Transfer-program (UICC)	
Finnish Association of Pathology	
Executive board	1985-1992
Chairman	1989-1991
Finnish Science Academy	
Finnish Cell Biology Association	
Societas Biochemica, Biophysica et Microbiologica Fennica	
American Society of Cell Biology	
American Association for Cancer Research	

Mentor for doctoral training:

1. Robert Winqvist: Chromosomal analysis of amplified oncogenes and *myc* protein, 1986.
2. Kalle Saksela: *myc* genes in human lung cancer: regulation and amplification, 1989.
3. Lea Sistonen: Regulation of gene expression by c-Ha-*ras* and *neu* oncoproteins, 1990.
4. Heikki Lehväslaiho: Functional analysis of the *neu* oncoprotein by recombinant DNA techniques, 1991.
5. Laura Lehtola: Analysis of the *neu* oncoprotein and other tyrosine kinases expressed in breast cancer cells, 1991.
6. Päivi Koskinen: Regulation and roles of c-*myc* and other growth factor-responsive genes, 1991.
7. Tomi Mäkelä: Studies on *myc* family and associated proteins: identification of the *rlf*-L-*myc* rearrangement, 1991.
8. Juha Partanen: Molecular cloning and characterization of novel tyrosine kinases expressed in K562 human leukemia cells, 1992.
9. Elina Armstrong: Analysis of chromosomal location and expression of novel leukemia cell receptor tyrosine kinase genes, 1993.
10. Harri Hirvonen: Of Myc and Men - expression of *MYC* proto-oncogenes in human fetal development, leukemias and brain tumors, 1993.
11. Liisa Pertovaara: Gene regulation by transforming growth factor-ß and inducers of tumor cell differentiation, 1994.
12. Jaana Korhonen: Characterization of endothelial receptor tyrosine kinases Tie and Flt4 in angiogenesis, 1995.
13. Katri Pajusola: Cloning and characterization of a new endothelial receptor tyrosine kinase Flt-4 and two novel VEGF-like growth factors VEGF-B and VEGF-C, 1996.
14. Imre Västrik: Max, ΔMax and Mad1 as regulations of Myc proteins, 1996.
15. Satu Vainikka: Signal Transduction and expression of FGF receptor-4, 1996.
16. Erika Hatva: Receptor tyrosine kinases and growth factors in human brain tumors and vascular malformations, 1996.
17. Arja Kaipainen: Molecular control of lymphangiogenesis: Role of VEGF-C and its receptors, 1997.
18. Juha Klefström: Oncogenes as regulators of tumor necrosis factor induced cell death, 1997.
19. Petri Salven: Angiogenic molecules and cancer. Role of the vascular endothelial growth factor family, 1998.
20. Birgitta Olofsson: Studies of the vascular endothelial growth factors, VEGFs, and their receptors focusing on VEGF-B, 1999.
21. Athina Lymboussakis: Vascular endothelial growth factors and their receptors in embryos, adults and tumors, 1999.

Invited speaker:

Recombinant DNA applications to defects in cellular functions and human diseases, 12.- 14.05.1985, Gentofte, ***Denmark***
Acta Endocrinologica Congress, 4.-10.08.1985, Helsinki, ***Finland***
EMBO Workshop on Oncogenes and Immortalization 4.-07.09.1985, Grignon, ***France***
Meeting of the Nordic Study Group on Cellular and Chemical Carcinogenesis, 14.-17.10.1985, Gl. Vrå, ***Denmark***
Maimonides Conference on Cancer Research, 1.-7.12.1985, Ein Gedi, ***Israel***
Chairman of the meeting "Role of Oncogenes in Human Cancer", 9.-10.01.1986, Helsinki, ***Finland***
European Tumor Virus Group Meeting, Chairman of the session "Cellular Oncogenes", 12.-19.04.1986, Le Normont, ***France***
Growth Factror Cascades: Mechanisms and opportunities for intervention, 15.-16.6.1986, Oslo, ***Norway***
Virus, Oncogenes et Cancer Humain, 21.4.1986, Villejuif, ***France***
IXV Annual Meeting of the International Society for Oncodevelopmental Biology and Medicine, 14.-17.08.1986, Helsinki, ***Finland***
Recombinant DNA in Clinical Medicine, 23.-26.8.1986, Hanasaari ***Finland***
First Conference on Differentiation Therapy 30.8.-3.9.1986, Capo Boi, ***Italy***
Cancer Prevention: Basic and Practical, 18.-19.10.1986, Hanasaari, ***Finland***
Growth Factors, Oncogenes and Cancer 22.-26.10.1986, Stockholm, ***Sweden***
EMBO Symposium on Oncogenes and Growth Control, 26.-30.4.1987, Heidelberg, ***Germany***
IX Meeting of the European Association for Cancer Research, 1.-3.6.1987, Helsinki, ***Finland***
Expression of Oncogenes and Regulation of Cell Growth, 5.-6.6.1987, Uppsala, ***Sweden***
Tumor Biology, Karolinska Institutet, 19.-20.8.1987, Stockholm, ***Sweden***
EACR Workshop on Oncogene Expression in Human Tumours 2.-4.9.1987, Cambridge, ***UK***
XII Berzelius Symposium: Growth Factors and Oncogenes – Structure, Function and Clinical Implications, 7.-8.9.1987, Sigtuna, ***Sweden***
Directions in Bioscience 11.-15.4.1988, Newark, ***USA***
XXI Nordiska Kongressen I Klinisk Kemi: Growth factors, oncogenes and cancer, 19.-22.6.1988, Kuopio, ***Finland***
European Tumor Virus Group Meeting, 30.4.-5.5.1989, Sundbyholm, ***Sweden***
Nordic Cancer Union Meeting, 17.-19.8.1989, Stockholm, ***Sweden***
EACR Oncogenes and Growth Control meeting 11.-12.9.1989, Galway, ***Ireland***
Molecular Basis of Human Cancer 13.-16.6.1990, Frederick, ***USA***
European Study Group on Cell Proliferation 13.9.1990, Espoo, ***Finland***
Oncogenes and Growth Control. The British Council 4.-7.6.1990, London, ***England***
Third European Congress on Cell Biology, 2.-5.9.1990, Firenze, ***Italy***
International Symposium on Angiogenesis, Chairman of the molecular biology session, 13.-15.3.1991, St. Gallen, ***Switzerland***
Scandinavian Breast Cancer Symposium 3.-5.6.1991, Haikko, ***Finland***
Sixth European Conference on Clinical Oncology and Cancer Nursing, 27.-31.10.1991, Firenze, ***Italy***
22nd Symposium of the Princess Takamatsu Cancer Research Fund, 19.-21.11.1991, Tokyo, ***Japan***
BACR Meeting on Growth Control and Cancer Therapy, 5.-7.12.1991, London, ***UK***
6th Congress of the European Society of Surgical Oncology, 10.-13.6.1992, Helsinki, ***Finland***
Growth Factor Receptors 15.-19.6.1992, Alpbach, ***Austria***
Molecular Basis of Human Cancer, 18.-21.6.1992, Frederick, ***USA***
egulatory Peptides of the Fibroblast Growth Factor Family, 11.-16.10.1992, Roscoff, ***France***

Mutant Oncogenes: Targets for Therapy 1992, 22-23.10.1992, London, *England*
Signalling mechanisms involved in control of cell growth; 3.-4.12.1992, London, *England*
8th International Symposium on Detection and Prevention of Human Cancer, 14.-18.3.1993, Nice, *France*
Phosphorylation/Dephosphorylation in Signal Transduction, 17.-24. 1.1993, Keystone, *USA*
XII Meeting of the European Association for Cancer Research, 4.-7.4.1993, Brussels, *Belgium*
European Congress on Biotechnology, 14.-16.6.1993, Firenze, *Italy*
The Molecular Basis of Cancer, 18.-20.6,1993, Frederick, *USA*
Ninth Annual Meeting on Oncogenes, 22.-26.6.1993, Frederick, *USA*
Growth Factors and Their Receptors, 16.-18.8.1993, Uppsala, *Sweden*
Cancer Symposium, 29.8-1.9.1993, Copenhagen, *Denmark*
Lympho-Hemopoiesis, 4.-7.9.1993, Ulm, *Germany*
Regulatory Molecules in Cell Proliferation, Cell Differentiation and Apoptosis, 10.-13.10.1993, Essen, *Germany*
Banbury Meeting on Mechanisms of Developmental and Tumor Angiogenesis. 7.-10.11.1993, Cold Spring Harbor, *USA*
Interactions of Cancer Susceptibility Genes and Environmental Carcinogens, 9.-13.11.1993, Lyon, *France*
Molecular Pathobiology of Cancer, 11-15 4.1994, Dalfsen, *The Netherlands*
Molecular and Cellular Aspects of FGFs and their Receptors, 29.5.-02.6.1994, Capri, *Italy*
FEBS Special Meeting on Biological Membranes, 26.6.-1.7.1994, Helsinki, *Finland*
Regulation of Hematopoietic Stem Cells, 18.-20.12.1994, Osaka, *Japan*
Human Hematopoietic Stem Cell Meeting, 31.3.-2.4.1995, Vienna, *Austria*
Cytoplasmic Protein-Tyrosine Kinases, 12.-14.5.1995, Stockholm, *Sweden*
Chairman of the EMBO Workshop on Growth Factors and Receptor Kinases, 26.-28.5.1995, Helsinki, *Finland*
The Frontiers of Contemporary Science, 5.-7.6.1995, Kuopio, *Finland*
3rd Meeting of the Federation of European Biochemical Societies, 13.-18.8.1995, Basel, *Switzerland*
International Society of Experimental Hematology, 27.-31.8.1995, Düsseldorf, *Germany*
Tumor angiogenesis and anti-angiogenesis, 1.-5.11.1995, Titisee, *Germany*
Keystone symposium on Signal Transduction through Tyrosine Kinases, 27.3.-2.4.1996, Taos, *USA*
Vascular Endothelium and Regulation of Leukocyte Traffic, 20-22.5.1996, Madrid, *Spain*
EMBO Practical Course on Growth and Differentiation Factors, 27.7.1996, Birmingham, *England*
Fourth International Workshop on Targeted Cancer Therapy, 21.-23.8.1996, Bethesda, Maryland, *USA*
Symposium on Vascular Remodeling, 14.9.1996, Tokyo, *Japan*
IX International Vascular Biology Meeting, 4.-8.9.1996, Seattle, *USA*
First Haartman Symposium on Cell Differentiation, 19.-21.9.1996 Helsinki, *Finland*
Development, Cell Differentiation and Cancer, 28.9.-2.10.1996, Pisa, *Italy*
The Role of Cytokines in Human Disease, 17.-20.11.1996, Tegernsee, *Germany*
AACR Conference on Cell Signalling and Cancer Treatment, 23.-28.2.1997, Telfs-Buchen, *Austria*
A lecturer of the Program of Ten-Year Cancer Control, 29.3.-6.4.1997, Tokyo, Kanazawa, Kumamoto, *Japan*
Gordon Conference on Angiogenesis and Microcirculation, 17.-22.8.1997, New Hampshire, *USA*
Wenner-Gren Symposium on Protein Phosphorylation, 4.-6.9.1997, Stockholm, *Sweden*
Cell Signaling and Tumor Angiogenesis, 9.-14.9.1997, Lake Placid, *USA*
The European Cancer Conference, 14.-18.9.1997, Hamburg, *Germany*
Philippe Laudat Conference, 21.-25.9.1997, Paris, *France*
Molecular Determinants of Cancer Metastasis, 28.-31.10.1997, Houston, *USA*
The Endothelial Cell, 14.11.1997, Paris, *France*
American Society of Hematology Annual Meeting, 3.-11.12.1998, San Diego, *USA*

Angiogenesis and Cancer, 24.-28.1.1998, Orlando, *USA*
Signal Transduction and Angiogenesis, 5.-8.2.1998, Paris, *France*
Ovarian Cancer - Basic Science and Modern Treatment, 20.3.1998, Tampere, *Finland*
Vascular Biology of Complications in Diabetes, 5.4.1998, Stockholm, *Sweden*
IBC/Angiogenesis Meeting 24.4.1998, Boston, *USA*
Angiogenesis Meeting, 27.5.1998, London, *England*
MDC Symposium, 6th Symposium on Gene Therapy, 4.-6.5.1998, Berlin-Buch, *Germany*
Vascular Complications in Diabetes, 30.4.1998, Stockholm, *Sweden*
EFES 2nd Postgraduate Course in Molecular and Cellular Endocrinology, 8.6.1998, Turku, *Finland*
Laboratory Medicine 98, XXVI Nordic Congress of Clinical Chemistry, 8.6.1998, Turku, *Finland*
Silver Jubilee FEBS Meeting, 5.-10.7.1998, Copenhagen, *Denmark*
Vascular Biology Conference 98, 24.-25.7.1998, Ohtsu, *Japan*
Gordon Research Conference on Peptide Growth Factors, 9.-14.8.1998, New Hampshire, *USA*
Xth International Vascular Biology Meeting, 23.-27.8.1998, Cairns, *Australia*
5th Franz-Volhard-Symposium, 3.-4.9.1998, Gross Dölln, *Germany*
First International Symposium on GIST, 25.-26.9.1998, Helsinki, *Finland*
10th Conference of the International Society of Differentiation, 3.-7.10.1998, Houston, *USA*
29th International Symposium of the Princess Takamatsu Cancer Research Fund, 17.-19.11.1998, Tokyo, *Japan*
Novel tools and methologies to promote or inhibit angiogenesis for drug development, 3.-4.12.1998, London, *England*
Role vascular endothelial growth factors in normal and pathological blood vessel formation, 18.-20.12.1998, Siena, *Italy*
UK Molecular Biology and Cancer Network meeting 15, 14.-16.12.1998, Warwick, *England*
NOVO Nordisk Ceremony, 24.-25.1.1999, Copenhagen, *Denmark*
ESF/EMRC Workshop on Proteome Analysis in Medical Research, 5.-7.2.1999, Chamonix, *France*
Annual Meeting of the Center for Molecular medicine (ZMMK), Signal Transduction and Disease, 13.-14.3.1999, Cologne, *Germany*
Danish Association for Cancer Research, Annual Meeting, 22-23.4.1999, Copenhagen, *Denmark*
International Titisee Conference, Parallels in cancer and embryonic development, 29.4.-2.5.1999, Titisee-Neustadt, *Germany*
EVBA meeting, Endothelial Cell Activation: Inflammation and Angiogenesis, 15.-16.5.1999, Baden, *Austria*
Ludwig Institute for Cancer Research, Angiogenesis meeting, 7.6.1999, Helsinki, *Finland*
European Developmental Biology Congress–99, 19.-23.6.1999, Oslo, *Norway*
UICC Conference on Cell Signaling and Cancer, 5.-8.8.1999, Tammsvik, *Sweden*
Gordon Conference on Angiogenesis and Microcirculation, Salve Regina University, 14.-21.8.1999, Newport, *USA*
VII Danish Cancer Society Symposium, 24.8.1999, Copenhagen, *Denmark*
The IXth Annual BioCity Symposium, From Receptor Activation to Gene Expression, 26.-27.8.1999, Turku, *Finland*
MMGM, Mouse Molecular Genetics Meeting, 4.9.1999, Heidelberg, *Germany*
European Meeting on Vascular Biology and Medicine, 29.-30.9.1999, Nürnberg, *Germany*
EMBO Workshop on Stem Cells, Growth Factors and Cancer, 7.-10.10.1999, Torino, *Italy*
IIGB Workshop on Vasculogenesis and Angiogenesis, 9.-12.10.1999, Capri, *Italy*
ESH Conference on Angiogenesis and Tumours, 22.-25.10.1999, Paris, *France*
International Society for Oncodevelopmental Biology and Medicine, 31.10.-4.11.1999, Kyoto, *Japan*
ASN Basic Science Conference, 2.-4.11.1999, Miami, *USA*
Workshop on Lymphoid Organogenesis, 5.11.1999, Basel, *Switzerland*
Biological basis for antiangiogenic therapy, 7.-10.11.1999, Milan, *Italy*

Angiogenesis Workshop, 11.11.1999, Basel, ***Switzerland***
Nordic Symposium of Radiation Oncology, 22.-24.11.1999, Tampere, ***Finland***

Opponent of doctoral dissertations:

Dr. Zvi Wirschubsky, Karolinska Institutet, Stockholm, Sweden, 1986
Dr. Sigurdur Ingvarsson, Karolinska Institutet, Stockholm, Sweden, 1989
Dr. Arne Östman, University of Uppsala, Uppsala, Sweden, 1990
Dr. Klaus Elenius, University of Turku, Turku, Finland, 1992
Dr. Berthe Willumsen, University of Copenhagen, Copenhagen, Denmark, 1993

the matrix of amniotic epithelial cells. ***EMBO J.*** 1: 47-52, 1982.

21. Keski-Oja, J., Gahmberg, C.G. and Alitalo, K.: Pericellular matrix and cell surface glycoproteins of virus-transformed mouse epithelial cells. ***Cancer Res.*** 42: 1147-1153, 1982.

2. Alitalo, K., Keski-Oja, J., Hedman, K. and Vaheri, A.: Loss of different pericellular matrix components of rat cells transformed by a T-class ts-mutant of Rous sarcoma virus. ***Virology*** 119: 347-357, 1982.

23. Majamaa, K., Myllylä, R., Alitalo, K. and Vaheri, A.: Regulation of proline 3-hydroxylation and prolyl 3-hydroxylase and 4-hydroxylase activities in transformed cells. ***Biochem. J.*** 206: 499-503, 1982.

24. Alitalo, K., Myllylä, R., Sage, H., Pritzl, P., Vaheri, A. and Bornstein, P.: Biosynthesis of type V collagen by A204, a human rhabdomyosarcoma cell line. ***J. Biol. Chem.*** 257: 9016-9024, 1982.

25. Alitalo, K., Bornstein, P., Vaheri, A. and Sage, H.: Biosynthesis of an unusual collagen type by human astrocytoma cells *in vitro*. ***J. Biol. Chem.*** 258: 2653-2661, 1983.

26. Sovova, V., Travnicek, M., Hlozanek, I., Cerna, H., Alitalo, K. and Vaheri, A.: Evidence for p15 cleavage site in *myc*-specific proteins of avian MC29 and OK10 viruses. ***J. Cell. Biochem.*** 28: 265-272, 1983.

27. Alitalo, K., Keski-Oja, J. and Bornstein, P.: Effects of Zn2+ ions on protein phosphorylation in epithelial cell membranes. ***J. Cell. Physiol.*** 115: 305-312, 1983.

28. Courtneidge, S., Ralston, R., Alitalo, K. and Bishop, J.M.: Subcellular location of an abundant substrate (p36) for tyrosine-specific protein kinases. ***Mol. Cell. Biol.*** 3: 340-350, 1983.

29. Alitalo, K., Bishop, J.M., Smith, D.H., Chen, E.Y., Colby, W.W. and Levinson, A.D.: Nucleotide sequence of the v-*myc* oncogene of avian retrovirus MC29. ***Proc. Natl. Acad. Sci.*** USA, 80: 100-104, 1983.

30. Alitalo, K., Schwab, M., Lin, C.C., Varmus, H. and Bishop, J.M.: Homogeneously staining chromosomal regions contain amplified copies of an abundantly expressed cellular oncogene (c-*myc*) in malignant neuroendocrine cells from a human colon carcinoma. ***Proc. Natl. Acad. Sci.*** USA, 80: 1707-1711, 1983.

31. Schwab, M., Alitalo, K., Varmus, H., Bishop, J.M. and George, D.: A cellular oncogene (c-Ki-*ras*) is amplified, overexpressed and located within karyotypic abnormalities in mouse adrenocortical tumour cells. ***Nature*** 303: 497-501, 1983.

32. Alitalo, K., Ramsay, G.M., and Bishop, J., Pfeifer-Ohlsson, S., Colby, W.W. and Levinson, A.D.: Identification of nuclear proteins encoded by viral and cellular *myc*-oncogenes. ***Nature*** 306: 274-277, 1983.

33. Schwab, M., Alitalo, K., Klempnauer, K.-H., Gilbert, F., Brodeur, G., Trent, J.T., Varmus, H.E. and Bishop, J.M.: Amplified DNA with limited homology to *myc* cellular oncogene is shared by human neuroblastoma cell lines and a neuroblastoma tumour. ***Nature*** 305: 245-248, 1983.

34. Alitalo, K., Winqvist, R., Lin, C.C., de la Chapelle, A., Schwab, M. and Bishop, J.M.: Aberrant expression of an amplified c-*myb* oncogene in two cell lines from a colon carcinoma. ***Proc. Natl. Acad. Sci.*** USA, 81: 4534-4538, 1984.

35. Lehto, V.-P., Virtanen, I., Ralston, R., Paasivuo, R. and Alitalo, K.: The p36 substrate of tyrosine-specific protein kinases co-localizes with non-erythrocyte alpha-spectrin antigen, p230, in surface lamina of cultured fibroblasts. ***EMBO J.*** 2: 1701-1705, 1983.

36. Winqvist, R., Saksela, K. and Alitalo, K.: *myc*-proteins are not associated with chromatin in mitotic cells. ***EMBO J.*** 3: 2947-2950, 1984.

37. Keski-Oja, J., Alitalo, K., Hautanen, A. and Rapp, U.R.: Transformation of cultured epithelial cells by ethylnitrosourea: altered expression of type I procollagen chains. ***Biochem. Biophys. Acta*** 803: 153-162, 1984.

38. Alitalo, K., Ralston, R.R. and Keski-Oja, J.: Distribution of the 36 000 dalton tyrosine protein kinase substrate in drug- and epidermal growth factor-treated epithelial cells. ***Exp. Cell Res.*** 150: 177-186, 1984.

39. Lin, C.C., Alitalo, K., Schwab, M., George, D., Varmus, H.E. and Bishop, M.: Evolution of karyotypic abnormalities and c-*myc* oncogene amplification in a human colonic carcinoma. ***Chromosoma*** 92: 11-15, 1985.

40. Saksela, K., Bergh, J., Lehto, V-P., Nilsson, K. and Alitalo, K.: Aplification of the c-*myc* oncogene is characteristic of a subpopulation of human small cell lung cancer. ***Cancer Res.*** 45: 1823-1827, 1985.

41. Winqvist, R., Knuutila, S., Leprince, D., Stehelin, D. and Alitalo, K.: Mapping of amplified c-*myb* oncogene, sister chromatid exchanges and karyotypic analysis of the COLO 205 colon carcinoma cell line. ***Cancer Genet. Cytogenet.*** 18: 251-264, 1985.

42. Pohjanpelto, P., Hölttä, E., Jänne, O., Knuutila, S. and Alitalo, K.: Amplification of ornithine decarboxylase gene in response to polyamine starvation in CHO cells. ***J. Biol. Chem.*** 260: 8532-8537, 1985.

43. Alitalo, K., Saksela, K., Winqvist, R., Laiho, M., Keski-Oja, J., Alitalo, R., Ilvonen, M., Knuutila, S., and de la Chapelle, A.: Acute myelogenous leukemia with c-*myc* amplification and double minute chromosomes. ***The Lancet II***: 1035-1038, 1985.

44. Keski-Oja, J. and Alitalo, K.: Reorganization of plasma membrane-associated 36 000 dalton protein upon drug-induced redistribution of cytokeratin. ***Exp. Cell. Res.*** 158: 86-95, 1985.

45. Schwab, M., Ramsay, G., Alitalo, K., Varmus, H.E., Bishop, J.M., Martinsson, T., Levan, G. and Levan A.: Amplification and enhanced expression of the c-*myc* gene in mouse SEWA cells. ***Nature*** 315: 345-347, 1985.

46. Schwab, M., Klempnauer, K.-H., Alitalo, K., Varmus, H. and Bishop, J.M.: Rearrangement at the 5' end of amplified c-*myc* in human COLO320 cells is associated with abnormal transcription. ***Mol. Cell. Biol.*** 6: 2752-2755, 1986.

47. Winqvist, R., Mäkelä,T.P., Seppänen, P., Jänne, O.A., Alhonen-Hongisto, L., Jänne, J., Grzeschik, K.-H. and Alitalo, K.: Human ornithine decarboxylase sequences map to chromosome regions 2pter - p23 and 7cen - qter but are not coamplified with the N-*myc* oncogene. ***Cytogenet. Cell Genet.*** 42: 133-140, 1986.

48. Alhonen-Hongisto, L., Leinonen, P., Sinervirta, R., Laine, R., Winqvist, R., Alitalo, K., Jänne, O.A. and Jänne, J.: Mouse and human ornithine decarboxylase genes: Methylation polymorphism and amplification. ***Biochem. J.*** 242: 205-210, 1987.

49. Sistonen, L., Keski-Oja, K., Ulmanen, I., Hölttä, E., Wikgren, B.-J. and Alitalo, K.: Dose effects of transfected c-Ha-*ras* (Val 12) oncogene in transformed cell clones. ***Exp. Cell Res.*** 168: 518-530, 1987.

50. Klinger, K.W., Winqvist, R., Riccio, A., Andreasen, P.A., Sartorio, R., Nielsen, L.S., Stuart, P., Stanislovits, P., Watkins, P., Douglas, R., Grzeschik, K.-H., Alitalo, K., Blasi, F. and Danø, K.: Plasminogen activator inhibitor type 1 gene is located at region q21.3-q22 of chromosome 7 and genetically linked with cystic fibrosis. ***Proc. Natl. Acad. Sci.*** USA 84: 8548-8552, 1987.

51. Alitalo, R., Andersson, L., Betsholtz, C., Nilsson, K., Westermark, B., Heldin, C.-H. and Alitalo, K.: Induction of platelet-derived growth factor gene expression during megakaryoblastic and monocytic differentiation of human leukemia cell lines. ***EMBO J.*** 6: 1213-1218, 1987.

52. Mäkelä, T.P., Alitalo, R., Paulsson, Y., Westermark, B., Heldin, C.-H. and Alitalo, K.: Regulation of platelet derived growth factor gene expression by transforming growth factor-ß and phorbol ester in human leukemia cell lines. ***Mol. Cell. Biol.*** 7: 3656-3662, 1987.

53. Sandberg, M., Vuorio, T., Hirvonen, H., Alitalo, K. and Vuorio, E.: Enhanced expression of TGFß and c-*fos* mRNAs in the growth plates of developing human long bones. ***Development*** 102: 461-470, 1988.

54. Vuorio, T., Rajamäki, A., Sandberg, M., Alitalo, K. and Vuorio, E.: Expression of the c-Ha-*ras* oncogene in DMBA-induced, antiestrogen-treated rat mammary tumors. ***Int. J. Cancer*** 42: 774-779, 1988.

55. Alitalo, R., Mäkelä, T.P., Andersson, L.C. and Alitalo, K.: Enhanced expression of transforming growth factor ß RNA:s during megakaryoblastic differentiation of K562 leukemia cells. ***Blood*** 71: 899-906, 1988.

56. Hölttä, E., Sistonen, L. and Alitalo, K.: The mechanisms of ornithine decarboxylase deregulation in c-Ha-*ras*-oncogene-transformed NIH 3T3 cells. ***J. Biol. Chem.*** 263: 4500-4507, 1988.

57. Legraverend, C., Potter, A., Hölttä, E., Alitalo, K. and Anderson, L.: Interleukin-2 regulates the expression of ornithine decarboxylase

in a cloned murine T lymphocytic cell line. ***Exp. Cell Res.*** 181: 273-281, 1989.

58. Hurme, M., Sihvola, M., Alitalo, K. and Keski-Oja, J.: Transforming growth factor ß does not alter interleukin-1 expression in cultured human macrophages. ***J. Cell. Biochem.*** 39: 467-475, 1989.

59. Sihvola, M, Sistonen, L., Alitalo, K. and Hurme, M.: Mechanism of T-cell proliferation *in vivo*: analysis of IL-2 receptor expression and activation of c-*myc* and c-*myb* oncogenes during lymphatic regeneration. ***Biochem. Biophys. Res. Commun.*** 160: 181-188, 1989.

60. Hirvonen, H., Sandberg, M., Kalimo, H., Hukkanen, V., Vuorio, E. and Alitalo, K.: The N-*myc* proto-oncogene and IGF-II growth factor mRNA:s are expressed by distinct cells in human fetal kidney and brain. ***J. Cell Biol.*** 108: 1093-1104, 1989.

61. Sistonen, L., Hölttä, E., Mäkelä, T. P., Keski-Oja, J. and Alitalo, K.: The cellular response to induction of the p21c-Ha-*ras* oncoprotein includes stimulation of *jun* gene expression. ***EMBO J.*** 8: 815-822, 1989.

62. Bianchi, N.O., Bianchi, M.S., Alitalo, K. and de la Chapelle, A.: The methylation pattern of normal and truncated amplified human c-*myc* oncogenes. ***Biochem. Biophys. Acta*** 1007: 350-355, 1989.

63. Saksela, K., Mäkelä, T. P., Evan, G. and Alitalo, K.: A rapid change in L-*myc* protein phosphorylation induced by phorbol ester tumor promoters and serum. ***EMBO J.*** 8: 149-157, 1989.

64. Sistonen L., Lehväslaiho H., Lehtola L., Hölttä E. and Alitalo K.: Activation of a chimeric EGF-R/*neu* tyrosine kinase induces the *fos/jun* transcription factor complex, glucose transporter and ornithine decarboxylase. ***J. Cell Biol.*** 109: 1911-1919, 1989.

65. Pandiella, A., Lehväslaiho, H., Magni, M., Alitalo, K. and Meldolesi, J.: Activation of an EGFR/*neu* chimeric receptor: intracellular signals and cell proliferation responses. ***Oncogene*** 4: 1299-1305, 1989.

66. Lehväslaiho H., Lehtola L., Sistonen L. and Alitalo K.: A chimeric EGF-R/*neu* proto-oncogene allows EGF to regulate *neu* tyrosine kinase and cell transformation. ***EMBO J.*** 8: 159 -166, 1989.

67. Pertovaara L., Sistonen L., Bos T., Vogt P., Keski-Oja J. and Alitalo, K.: Enhanced *jun* gene expression is an early genomic response to transforming growth factor-ß stimulation. ***Mol. Cell. Biol.*** 9: 1255-1262, 1989.

68. Mäkelä, T.P., Saksela, K. and Alitalo, K.: Two N-*myc* polypeptides with distinct amino termini encoded by the second and third exons of the gene. ***Mol. Cell. Biol.*** 9: 1545-1552, 1989.

69. Lehtola, L., Lehväslaiho, H., Sistonen, L., Beguinot, L. and Alitalo, K.: Receptor downregulation and DNA synthesis are modulated by EGF and TPA in cells expressing an EGFR/*neu* chimera. ***Growth Factors*** 1: 323-334, 1989.

70. Saksela, K., Mäkelä, T.P. and Alitalo, K.: Oncogene expression in small cell lung cancer cell lines and a testicular germ-cell tumor: Activation of the N-*myc* gene and decreased RB mRNA. ***Int. J. Cancer*** 44: 182-185, 1989.

71. Bianchi, N.O., Bianchi, M.S., López-Larraza, D., Alitalo, K. and de la Chapelle, A.: Damage and repair induced by bleomycin in the domain of human amplified *myc* oncogenes. ***Cancer Res.*** 50: 2379-2384, 1990.

72. Lehväslaiho, H., Sistonen, L., diRenzo, F., Partanen, J., Comoglio, P., Hölttä, E. and Alitalo, K.: Regulation by EGF is maintained in an overexpressed chimeric EGFR/*neu* tyrosine kinase. ***J. Cell. Biochem.*** 42: 123-133, 1990.

73. Sistonen L., Koskinen P., Lehväslaiho H., Lehtola L., Bravo R. and Alitalo K.: Downregulation of the early genomic growth factor response in *neu* oncogene-transformed cells. ***Oncogene*** 5: 815-821, 1990.

74. Koskinen, P., Lehväslaiho, H., MacDonald-Bravo, H., Alitalo, K. and Bravo, R.: Similar early gene responses to ligand-activated EGFR and *neu* tyrosine kinases in NIH 3T3 cells. ***Oncogene*** 5: 615-618, 1990.

75. Laitinen, J., Sistonen, L., Alitalo, K. and Hölttä, E.: c-Ha-*ras*^{Val12}oncogene-transformed NIH-3T3 fibroblasts display more decondensed nucleosomal organization than normal fibroblasts. ***J. Cell Biol.*** 111: 9-17, 1990.

76. Alitalo, R., Partanen, J., Pertovaara, L., Hölttä, E., Sistonen, L., Andersson, L. and Alitalo, K.: Incresed erythroid potentiating activity/tissue inhibitor of metalloproteinases and *jun/fos* transcription factor complex characterize tumor promoter-induced

megakaryoblastic differentiation of K562 leukemia cells. ***Blood*** 75: 1974-1982, 1990.

77. Hirvonen, H., Mäkelä, T., Sandberg, M., Kalimo, H., Vuorio, E. and Alitalo, K.: Expression of the *myc* proto-oncogenes in developing human fetal brain. ***Oncogene*** 5: 1787-1797, 1990.

78. Partanen, J., Mäkelä, T.P., Alitalo, R., Lehväslaiho, H. and Alitalo, K.: Putative tyrosine kinases expressed in K-562 human leukemia cells. ***Proc. Natl. Acad. Sci.*** 87: 8913-8917, 1990.

79. Koskinen, P., Sistonen, L., Evan, G., Morimoto, R. and Alitalo, K.: Nuclear colocalization of cellular and viral *myc* proteins with HSP70 in *myc* overexpressing cells. ***J. Virol.*** 65: 842-851, 1991.

80. Saksela, K., Koskinen, P. and Alitalo, K.: Binding of a nuclear factor to the upstream region of the c-*myc* gene. ***Oncogene Res.*** 6: 73-76, 1991.

81. Lehtola, L., Sistonen, L., Koskinen, P.J., Lehväslaiho, H., Di Renzo, M.F., Comoglio, P.M. and Alitalo, K.: Constitutively activated *neu* oncoprotein tyrosine kinase interferes with growth factor-induced signals for gene activation. ***J. Cell. Biochem.*** 45: 69-81, 1991.

82. Partanen, J., Mäkelä, T., Eerola, E., Korhonen, J., Hirvonen, H., Claesson-Welsh, L. and Alitalo, K.: FGFR-4, a novel acidic fibroblast growth factor receptor with a distinct expression pattern. ***EMBO J.*** 10: 1347-1354, 1991.

83. Mäkelä, T.P., Saksela, K., Evan, G. and Alitalo, K.: A fusion protein formed by L-*myc* and a novel gene in lung cancer. ***EMBO J.*** 10: 1331-1335, 1991.

84. Mäkelä, T.P., Kere, J., Winqvist, R. and Alitalo, K.: Intrachromosomal rearrangement fusing L-*myc* and *rlf* in small cell lung cancer. ***Mol. Cell Biol.*** 11: 4015-4021, 1991.

85. Partanen, J., Eerola, E., Bergman, M., Mäkelä, T.P., Hirvonen, H., Huebner, H. and Alitalo, K.: *Cyl* encodes a putative cytoplasmic tyrosine kinase lacking the conserved tyrosine autophosphorylation site (Y416^{src}). ***Oncogene*** 6, 2013-2018, 1991.

86. Wärri, A.M., Laine, A.M., Majasuo, K.E., Alitalo, K. and Härkönen, P.L.: Enhanced *erb*B2 expression in association of growth arrest of ?R 75-1 human breast cancer cells *in vitro* and in nude mice tumors. ***Int. J. Cancer***, 49, 616-623, 1991.

87. Armstrong, E., Hästbacka, J., Partanen, J., Huebner, K. and Alitalo, K.: RFPLs in the fibroblast growth factor receptor-4 locus in 5q33-qter. ***Nucl. Acids Res.*** 19, 5096, 1991.

88. Koskinen, P.J., Sistonen, P., Bravo, R. and Alitalo, K. : Immediate early gene responses of NIH3T3 fibroblasts and NMuMG epithelial cells to TGFß. ***Growth Factors*** 5: 283-293, 1991.

89. Lehtola, L., Nister, M., Hölttä, E., Westermark, B. and Alitalo, K.: Down-regulation of cellular platelet-derived growth factor receptors induced by an activated *neu* receptor tyrosine kinase. ***Cell Regul.*** 2: 651-661, 1991.

90. Bianchi, N.O., Bianchi, M.S., Alitalo, K. and de la Chapelle, A.: UV damage and repair in the domain of the human c-*myc* oncogene. ***DNA and Cell Biol.*** 10: 125-132, 1991.

91. Armstrong, E., Partanen, J., Cannizzaro, L., Huebner, K. and Alitalo, K.: Localization of fibroblast growth factor receptor-4 gene to chromosome 5q33-qter. ***Genes, Chromos. Cancer***, 4: 94-98, 1992.

92. Saksela, K., Mäkelä, T.P., Hughes, K., Woodgett, J.R. and Alitalo, K.: Activation of PKC increases phosphorylation of the L-*myc* trans-activator domain at a GSK-3 target site. ***Oncogene*** 7: 347-353, 1992.

93. Mäkelä, T. P., Shiraishi, M., Borrello, M.G., Sekiya, T. and Alitalo, K.: Rearrangement and coamplification of L-*myc* and *rlf* in primary lung cancer. ***Oncogene*** 7: 405-409, 1992.

94. Aprelikova, O., Pajusola, K., Partanen, J., Armstrong, E., Alitalo, R., Bailey, S.K., McMahon, J., Wasmuth, J., Huebner, K. and Alitalo, K.: *FLT4*, a novel class III receptor tyrosine kinase in chromosome 5q33-qter. ***Cancer Res.*** 52: 746-748, 1992.

95. Partanen J., Armstrong E., Mäkelä T.P., Korhonen J., Sandberg M., Renkonen R., Knuutila S., Huebner K. and Alitalo K.: A novel endothelial cel surface receptor tyrosine kinase with extracellular epidermal growth factor homology domains. ***Mol. Cell Biol.*** 12: 1698-

1707, 1992.

96. Sekido, Y., Takahashi, T., Mäkelä, T. P., Obata, Y., Ueda, R., Hida, T., Kenja, H., Shimokata, K., Alitalo, K. and Takahasi, T.: Complex intrachromosomal rearrangement in the process of amplification of the L-*myc* gene in small cell lung cancer. ***Mol. Cell Biol.*** 12: 1747-1754, 1992.

97. Armstrong, E., Cannizzaro, L., Bergman, M., Huebner, K. and Alitalo, K.: The c-*src* tyrosine kinase (CSK) gene, a potential antioncogene localizes to human chromosome region 15q23-q25. ***Cytogen. Cell Gen.*** 60:119-120, 1992.

98. Mäkelä, T.P., Hellsten, E., Sajantila, A., Alitalo, K. and Peltonen, L.: An Alu variable polyA repeat polymorphism upstream of L-*myc* at 1p32. ***Hum. Mol. Gen.*** 1: 217, 1992.

99. Korhonen, J., Partanen, J., Armstrong, E. and Alitalo, K. Expression of the FGFR-4 mRNA in developing mouse tissues. ***Int. J. Devel. Biol.*** 36: 323-329, 1992.

100. Mäkelä, T.P., Koskinen, P., Västrik, I. and Alitalo, K.: Alternative forms of Max as enhancers or suppressors of *myc-ras* cotransformation. ***Science*** 256: 373-377, 1992.

101. Bergman, M., Mustelin, T., Oetken, C., Partanen, J., Flint, N.A., Amrein, K.E., Autero, M., Burn, P. and Alitalo, K.: The human p50*csk* tyrosine kinase phosphorylates p56*lck* at Tyr-505 and down-regulates its catalytic activity. ***EMBO J.*** 11: 2919-2924, 1992.

102. Lehtola, L., Partanen, J., Sistonen, L., Korhonen, J., Wärri, A., Härkönen, P., Clarke, R. and Alitalo, K.: Analysis of tyrosine kinase mRNAs including four FGF receptor mRNAs expressed in MCF-7 breast-cancer cells. ***Int. J. Cancer*** 50: 598-603, 1992.

103. Warrington, J.A., Bailey, S.K., Armstrong, E., Aprelikova, O., Alitalo, K., Dolganov, G.M., Wilcox, A., Sikela, J., Wolf, S.F., Lovett, M. and Wasmuth, J.J.: A radiation hybrid map of 18 growth factor, growth factor receptor, hormone receptor or neurotransmitter receptor genes on the distal region of the long arm of chromosome 5. ***Genomics*** 13: 803-808, 1992.

104. Pajusola, K., Aprelikova, O., Korhonen, J., Kaipainen, A., Pertovaara, L., Alitalo, R. and Alitalo, K.: FLT4 receptor tyrosine kinase contains seven immunoglobulin-like loops and is expressed in multiple human tissues and cell lines. ***Cancer Res.*** 52: 5738-5743, 1992.

105: Vainikka, S., Partanen, J., Bellosta, P., Coulier, F., Basilico, C., Jaye, M. and Alitalo, K.: Fibroblast growth factor receptor-4 shows novel features in genomic structure, ligand binding and signal transduction. ***EMBO J.*** 11: 4273-4280, 1992.

106. Mäkelä T. P., Partanen J., Schwab M. and Alitalo K.: Plasmid pLTRpoly: a versatile high efficiency mammalian expression vector. ***Gene*** 118: 293-294, 1992.

107. Korhonen, J., Partanen, J., Armstrong, E., Vaahtonen, A., Elenius, K., Jalkanen, M. and Alitalo, K.: Enhaced expression of the *tie* receptor tyrosine kinase in endothelial cells during neovascularization. ***Blood*** 80: 2548-2555,1992.

108. Pertovaara, L., Tienari, J., Vainikka, S., Partanen, J., Saksela, O., Lehtonen, E. and Alitalo, K.: Modulation of fibroblast growth factor receptor expression and signalling during retionic acid-induced differentiation of Tera-2 teratocarcinoma cells. ***Biochem. Biophys Res. Commun.*** 191: 149-156, 1993.

109. Maglione, D., Guerriero, V., Viglietto, G., Ferraro, M.G., Aprelikova, O., Alitalo, K., Del Vecchio, S., Lei, K-J., Chou, J.Y. and Persico, M.G.: Two alternative mRNAs coding for the angiogenic factor, placenta growth factor (PlGF), are transcribed from a single gene of chromosome 14. ***Oncogene*** 8: 925-931, 1993.

110. Pertovaara, L., Saksela, O. and Alitalo, K.: Enchanced bFGF gene expression in response to transforming growth factor b stimulation of AKR-2B cells. ***Growth Factors*** 9: 81-86, 1993.

111. Mummery, C.L., van Rooyen, Bracke, M., van den Eijnden-van Raaij, J., van Zoelen, E.J. and Alitalo, K.: Fibroblast growth factor-mediated growth regulation and receptor expression in embryonal carcinoma and embryonic stem cells and human germ cell tumours. ***Biochem. Biophys. Res. Commun.*** 191: 188-195, 1993.

112. Tamagnone, L., Partanen, J., Armstrong, E., Lasota, J., Ohgami, K. Tazunoki, T., LaForgia, S., Huebner, K. and Alitalo, K.: The human *ryk* cDNA sequence predicts a protein containing two putative transmembrane segments and a tyrosine kinase catalytic domain. ***Oncogene*** 8: 2009-2014, 1993.

113. Armstrong, E., Kastury, K., Pajusola, K., Aprelikova, O., Bullrich, F., Nezelof, C., Gorusev, J., Wasmuth, J.J., Alitalo, K., Morris, S. and Huebner, K.: FLT-4 receptor tyrosine kinase gene: mapping to chromosome 5q35 in relation to the t(2;5), t(5;6) and t(3;5) translocations. *Genes, Chromos. Cancer* 7: 144-151, 1993.

114. Polvi A., Armstrong, E. Lai, G., Lemke, G., Huebner, K., Spritz, R.A., Guida, L.C., Nicholls, R.D. and Alitalo, K.: The human TYRO3 gene and pseudogene are located in chromosome 15q14-q25. *Gene* 134: 289-293, 1993.

115. Klefström, J., Koskinen, P. J., Saksela. E., Jäättelä, M., Bravo, R. and Alitalo, K.: A subset of immediate early mRNAs induced by tumor necrosis factor-α during cellular cytotoxic and non-cytotoxic responses. *Int. J. Cancer* 55: 655-659, 1993.

116. Kaipainen, A., Korhonen, J., Pajusola, K., Aprelikova, O., Persico, M.G., Terman, B.I. and Alitalo, K. The Related FLT4, FLT1 and KDR receptor tyrosine kinases show distinct expression patterns in human fetal endothelial cells. *J. Exp. Med.* 178: 2077-2088, 1993.

117. Pajusola, K., Aprelikova, O., Armstrong, E., Morris, S. and Alitalo, K.: Two human FLT4 receptor tyrosine kinase isoforms with distinct carboxy terminal tails are produced by alternative processing of primary transcripts. *Oncogene* 8: 2931-2937, 1993.

118. Hellsten, E., Vesa, J., Speer, M., Mäkelä, T.P., Järvelä, I., Alitalo, K., Ott, J. and Peltonen, L.: Refined assigment of the infantile neuronal ceroid lipofuscinosis (INCL, CLN1) locus at 1p32: incorporation of linkage disequilibrium in multipoint analysis. *Genomics* 16: 720-725, 1993.

119. Korhonen, J., Polvi, A., Partanen, J. and Alitalo, K. The mouse *tie* receptor tyrosine kinase gene: Expression during embryonic angiogenesis. *Oncogene* 9: 395-403, 1994.

120. Autero, M., Saharinen, J., Pessa-Morikawa, T., Soula-Rothhut, M., Oetken, C., Gassmann, M., Bergman, M., Alitalo, K., Burn, P., Gahmberg, C.G. and Mustelin, T.: Tyrosine phosphorylation of CD45 phosphotyrosine phosphatase by $p50^{csk}$ kinase creates a binding site for $p56^{lck}$ tyrosine kinase and activates the phosphatase. *Mol. Cell. Biol.* 14: 1308-1321, 1994.

121. Pertovaara, L., Kaipainen, A., Mustonen, T., Orpana, A., Ferrara, N., Saksela, O. and Alitalo, K.: Vascular endothelial growth factor is induced in response to transforming growth factor-ß in fibroblastic and epithelial cells. *J. Biol Chem.*, 269: 6271-6274, 1994.

122. Vainikka, S., Joukov, V., Wennström, S., Bergman, M., Pelicci, P.G. and Alitalo, K.: Signal transduction by fibroblast growth factor receptor-4 (FGFR-4): Comparison with FGFR-1. *J. Biol. Chem.* 269: 18320-18326, 1994.

123. Oetken, C., Couture, C., Bergman, M., Bonnefoy-Bérard, N., Williams, S., Alitalo, K., Burn P. and Mustelin, T.: TCR/CD3-triggering causes increased activity of the p50csk tyrosine kinase and engagement of its SH2 domain. *Oncogene* 9: 1625-1631, 1994.

124. Philipp, A., Schneider, A., Västrik, I., Finke, K., Xiong, Y., Beach, D., Alitalo, K. and Eilers, M.: Repression of cyclin D1: a novel function of MYC. *Mol. Cell Biol.* 14: 4032-4043, 1994.

125. Koskinen, P., Västrik, I., Mäkelä, T.P., Eisenman, R.N. and Alitalo, K.: Max acitivty is affected by phosphorylation at two aminoterminal sites. *Cell Growth Differ.* 5: 313-320, 1994.

126. Maclean-Hunter, S., Mäkelä, T., Grzeschizek, A., Alitalo, K. and Möröy, T.: Expression of a RLF/L-*myc* minigene inhibits differentiation of embryonic stem cells and causes early embryonic lethality in transgenic mice. *Oncogene* 9: 3509-3517, 1994.

127. Tamagnone, L., Lahtinen, I., Mustonen, T., Virtaneva, K., Francis, F., Muscatelli, F., Alitalo, R., Smith, E.C.I., Larsson, C. and Alitalo, K.: *BMX*, a novel nonreceptor tyrosine kinase gene of the *BTK/ITK/TEC/TXK* family located in chromosome Xp22.2. *Oncogene*, 9:3683-3688, 1994.

128. Pajusola K., Aprelikova O., Pelicci G., Weich H., Claesson-Welsh L. and Alitalo K.: Signalling properties of FLT4, a proteolytically processed receptor tyrosine kinase related to two VEGF receptors. *Oncogene* 9: 3545-3555, 1994.

129. Klefström, J. Västrik, I., Saksela, E., Valle, J., Eilers, M. and Alitalo, K.: c-Myc induces cellular susceptibility to the cytotoxic action of TNF-α. *EMBO J.* 13: 5442-5450, 1994.

130. Koegel, M., Kypta, R.M., Bergman, M., Alitalo, K. and Courtnedge, S.A.: Rapid and efficient purification of SH2 domain-containing proteins: FYN, CSK and phosphatidylinositol 3-kinase p85. *Biochem. J.* 302: 737-744, 1994.

131. Kaipainen, A., Vlaykova, T., Hatva, E., Böhling, T., Jekunen, A., Pyrhönen, S. and Alitalo, K.: Enhanced expression of the *tie* receptor tyrosine kinase messenger RNA in the vascular endothelium of metastatic melanomas. ***Cancer Res.*** 54: 6571-6577, 1994.

132. Cance, W.G., Craven, Bergman, M., R.J., Xu, L.-H., Alitalo, K. and Liu, E.T.: Rak, a novel nuclear tyrosine kinase, expressed in epithelial cells. ***Cell Growth Differ.*** 5: 1347-1355, 1994.

133. Laitinen, J., Sistonen, L., Alitalo, K. and Hölttä, E.: Cell Transformation by c-Ha-*ras*^{Val12} oncogene is accompanied by a decrease in histone H1° and an increase in nucleosomal repeat length. ***J. Cell Biochem.*** 57: 1-11, 1995.

134. Hellsten, E., Vesa, J., Speer, M.C., Mäkelä, T.P., Järvelä, I. Alitalo, K., Ott, J. and Peltonen, L.: Refined assignment of the infantile neuronal ceroid lipofuscinosis (INCL, CLN1) locus at 1p32: incorporation of linkage disequilibrium in multipoint analysis. ***Genomics*** 16: 720-725, 1995.

135. Hatva, E., Kaipainen, A., Jääskeläinen, J., Haltia, M. and Alitalo, K.: Expression of endothelial cell-specific receptor tyrosine kinases and growth factors in human brain tumors. ***Am. J. Pathol.*** 146: 368-378, 1995.

136. Kaipainen, A., Korhonen, J., Mustonen, T., van Hinsbergh, V.W.M., Fang, G.-H., Dumont, D., Breitman, M. and Alitalo, K.: Expression of the fms-like tyrosine kinase 4 gene becomes restricted to lymphatic endothelium during development. ***Proc. Natl. Acad. Sci.*** 92: 3566-3570, 1995.

137. Bergman, M., Joukov, V., Virtanen, I. and Alitalo, K.: Overexpressed Csk tyrosine kinase is localized in focal adhesions, causes reorganization of αvβ5 integrin, and interferes with HeLa cell spreading. ***Mol. Cell Biol.*** 15: 711-722, 1995.

138. Dumont, D.J., Fong, G.-H., Puri, M., Gradwohl, G., Alitalo, K. and Breitman, M.: Vascularization of the mouse embryo: A study of *flk-1*, *tek*, *tie* and VEGF expression during development. ***Devel. Dynamics*** 203: 80-92, 1995.

139. Västrik, I., Kaipainen, A., Penttilä, T.-L., Lymboussakis, A., Alitalo, R., Parvinen, M. and Alitalo, K.: Expression of the *mad* gene during cell differentiation in vivo and its inhibition of cell growth in vitro. ***J. Cell Biol.*** 128: 1197-1208, 1995.

140. Västrik, I., Mäkelä, T.P., Koskinen, P.J. and Alitalo, K.: Determination of sequences responsible for the differential regulation of Myc function by deltaMax and Max. ***Oncogene*** 11: 553-560, 1995.

141. Ruohola, J.K., Valve, E.M., Vainikka, S., Alitalo, K. and Härkönen, P.L.: Androgen and fibroblast growth factor (FGF) regulation of the FGF receptors in S115 mouse mammary tumor cells. ***Endocrinology*** 136: 2179-2188, 1995.

142. Korhonen, J., Lahtinen, I., Halmekytö, M., Alhonen, L., Jänne, J., Dumont, D. and Alitalo, K.: Endothelial-specific gene expression directed by the *TIE* gene promoter in vivo. ***Blood*** 86: 1828-1835, 1995.

143. Hellsten, E., Vesa, J., Heiskanen, M., Mäkelä, T.P., Järvelä, I., Cowell, J.K., Mead, S., Alitalo, K., Palotie, A. and Peltonen, L.: Identification of YAC clones for human chromosome 1p32 and physical mapping of the infantile neuronal ceroid lipofuscinosis (INCL) locus. ***Genomics*** 25: 404-412, 1995.

144. Puri, M.C., Rossant, J., Alitalo, K., Bernstein, A. and Partanen, J.: The receptor tyrosine kinase Tie is required for the integrity and survival of vascular endothelial cells. ***EMBO J.*** 14: 5884-5891, 1995.

145. Mäkelä, T.P., Hellsten, E., Vesa, J., Hirvonen, H., Palotie, A., Peltonen, L., Alitalo, K. The rearranged L-*myc* fusion gene (*RLF*) encodes a Zn-15 related zinc finger protein. ***Oncogene*** 11: 2699-2704, 1995.

146. Laan, M., Kallioniemi, O.P., Hellsten, E., Alitalo, K., Peltonen, L. and Palotie, A.: Mechanically stretched chromosomes as targets for high resolution FISH mapping. ***Genome Res.*** 5: 13-20,1995.

147. Heiskanen, M., Hellsten, E., Kallioniemi, O-P, Mäkelä, T.P., Alitalo, K., Peltonen, L. and Palotie, A.: Visual mapping by fiber-FISH. ***Genomics*** 30: 31-36, 1995.

148. Batard, P., Sansilvestri, P., Schneinecker, C., Knapp, W., Debili, N., Vainchenker, W., Bühring, H-J., Monier, M-N., Kukk, E., Partanen, J., Matikainen, M-T., Alitalo, R., Hatzfeld, J. and Alitalo, K.: The Tie Receptor Tyrosine Kinase is Expressed by Human Hematopoietic Progenitor Cells and by a Subset of Megakaryocytic Cells. ***Blood*** 87: 2212-2220, 1996.

149. Joukov, V. , Pajusola, K., Kaipainen, Chilov, D., A., Lahtinen, I., Kukk, E., Saksela, O., Kalkkinen, N. and Alitalo, K.: A novel vascular endothelial growth factor, VEGF-C, is a ligand for the Flt4 (VEGFR-3) and KDR (VEGFR-2) receptor tyrosine kinases. ***EMBO J.*** 15: 290-298, 1996.

50. Vainikka, S., Joukov, V., Klint, P. and Alitalo, K. Association of a 85 kD Serine Kinase with Activated Fibroblast Growth Factor Receptor-4 (FGFR-4). ***J. Biol. Chem.*** 271: 1270-1273, 1996.

151. Hatva, E., Böhling, T, Jääskeläinen, J., Persico, M-G., Haltia, M. and Alitalo, K.: Vascular growth factors and receptors in capillary hemangioblastomas and hemangiopericytomas. ***Am. J. Pathol.*** 148: 763-775, 1996.

152. Olofsson, B.*, Pajusola, K.*, Kaipainen, A., von Euler, G., Joukov, V., Saksela, O., Orpana, A., Pettersson, R.F., Alitalo, K.* and Eriksson, U.*: Vascular endothelial growth factor B, a novel growth factor for endothelial cells. (* contributed equally to this work). ***Proc. Natl. Acad. Sci.*** 93: 2576-2581, 1996.

153. Paavonen, K., Horelli-Kuitunen, N., Chilov, D., Kukk, E., Pennanen, S., Kallioneimi, O.-P., Pajusola, K., Olofsson, B., Eriksson, U., Joukov, V., Palotie, A. and Alitalo, K.: Novel human vascular endothelial growth factor genes VEGF-B and VEGF-C localize to chromosomes 11q13 and 4q34, respectively. ***Circulation*** 93: 1079-1082, 1996.

154. Böhling, T., Hatva, E., Kujala, M., Claesson-Welsh, L., Alitalo, K. and Haltia, M: Expression of growth factors and growth factor receptors in capillary hemangioblastoma. ***J Neuropathol. Exp. Neurol.*** 55: 522-527, 1996.

155. Salvén, P., Joensuu, H., Heikkilä, P., Matikainen, M-T., Wasenius V-M., Alanko, A. and Alitalo, K.: Endothelial Tie growth factor receptor provides antigenic marker for assessment of breast cancer angiogenesis. ***Brit. J. Cancer*** 74: 69-72, 1996.

156. Kaukonen, J., Lahtinen, I., Laine, S., Alitalo, K.and Palotie, A.: *BMX* tyrosine kinase gene is expressed in granulocytes and myeloid leukaemias. ***Brit. J. Haematol.*** 94: 455-460, 1996.

157. Hatva, E., Jääskeläinen, J., Hirvonen, H., Alitalo, K.and Haltia, M.: Tie endothelial cell-specific receptor tyrosine kinase is upregulated in the vasculature of arteriovenous malformations. ***J. Neuropathol. Exp. Neurol.*** 55: 1124-1133, 1996.

158. Olofsson, B., Pajusola, K., von Euler, G., Chilov, D., Alitalo, K. and Eriksson, U.: Genomic organization of the mouse and human genes for vascular endothelial growth factor B (VEGF-B) and characterization of a second splice isoform. ***J. Biol. Chem.*** 271: 19310-19317, 1996.

159. Kukk, E., Lymboussaki, A., Taira, S., Kaipainen, A., Jeltsch, M., Joukov, V. and Alitalo, K.: VEGF-C receptor binding and pattern of expression with VEGFR-3 suggests a role in lymphatic vascular development. ***Development*** 122: 3829-3837, 1996.

160. Joukov, V., Vihinen, M., Vainikka, S., Sodawski, J. M., Alitalo, K. and Bergman, M.: Identification of Csk tyrosine phosphorylation sites and a tyrosine residue important for kinase domain structure. ***Biochem. J.*** 322: 927-935, 1997.

161. Enholm, B., Paavonen, K., Ristimäki, A., Kumar, V., Gunji, Y., Klefström, J., Kivinen, L., Laiho, M., Olofsson, B., Joukov, V., Eriksson, U. and Alitalo, K.: Comparison of VEGF, VEGF-B, VEGF-C and Ang-1 mRNA regulation by serum, growth factors, oncoproteins and hypoxia. ***Oncogene*** 14: 2475-2483, 1997.

162. Kukk, E., Wartiovaara, U., Gunji, Y., Kaukonen, J. Bühring, H.-J., Rappold, I., Matikainen, M.-T., Vihko, P., Partanen, J., Palotie, A. and Alitalo, K.: Analysis of Tie receptor tyrosine kinase in haemopoietic progenitor and leukaemia cells. ***Brit. J. Haematol.*** 98: 195-203, 1997.

163. Rappold, I., Ziegler, B.L., Köhler, I., Marchetto, S., Rosnet, O., Birnbaum, D., Simmons, P.J., Zannettino, A.C.W., Hill, B., Neu, S., Knapp, W., Alitalo, R., Alitalo, K., Ullrich, A., Kanz, L. and Bühring, H.-J.: Functional and phenotypic characterization of cord blood and bone marrow subsets expressing FLT3 (CD135) receptor tyrosine kinase. ***Blood*** 90: 111-125, 1997.

164. Salvén, P.J., Mäenpää, H.O., Orpana, A.O., Alitalo, K.K. and Joensuu, H.T.: Serum vascular endothelial growth factor is often elevated in disseminated cancer. ***Clin. Cancer Res.*** 3: 647-651, 1997.

165. Joukov, V., Sorsa, T., Kumar, V., Jeltsch, M., Claesson-Welsh, L., Cao, Y., Saksela, O., Kalkkinen, N. and Alitalo, K.: Proteolytic processing regulates receptor specificity and activity of VEGF-C. ***EMBO J.*** 16: 3898-3911, 1997.

166. Vuorela, P., Hatva, E., Lymboussaki, A., Kaipainen, K., Joukov, V., Persico, M.G., Alitalo, K. and Halmesmäki, E.: Expression of vascular endothelial growth factor and placenta growth factor in human placenta. ***Biol. Reprod.*** 56: 489-494, 1997.

167. Monni, O., Joensuu, H., Franssila, K.O., Klefström, J., Alitalo, K. and Knuutila, S.: BCL2 overexpression associated with chromosomal amplification in diffuse large B-Cell lymphoma. ***Blood*** 90: 1168-1174, 1997.

168. Jeltsch, M., Kaipainen, A., Joukov, V., Meng, X., Lakso, M., Rauvala, H., Swartz, M., Fukumura, D., Rakesh, K.J. and Alitalo, K.: Hyperplasia of lymphatic vessels in VEGF-C transgenic mice. ***Science*** 276: 1423-1425, 1997.

169. Oh, S.J., Jeltsch, M.M., Birkenhäger, R., McCarthy, J.E.G., Weich, H.A., Christ, B., Alitalo, K. and Wilting, J.: VEGF and VEGF-C: Specific induction of angiogenesis and lymphangiogenesis in the differentiated avian chorioallantoic membrane. ***Dev. Biol.*** 188: 96-109, 1997.

170. Chilov, D., Kukk, E., Taira, S., Jeltsch, M., Kaukonen, J., Palotie, A., Joukov, V. and Alitalo, K.: Genomic organization of human and mouse genes for vascular endothelial growth factor C. ***J Biol. Chem.*** 272: 25176-25183, 1997.

171. Ekman, N., Lymboussaki, A., Västrik, I., Sarvas, K., Kaipainen, A. and Alitalo, K.: Bmx tyrosine kinase is specifically expressed in the endocardium and the endothelium of large arteries. ***Circulation*** 96: 1729-1732, 1997.

172. Saharinen, P., Ekman, N, Sarvas, K., Parker, P., Alitalo, K. and Silvennoinen, O.: The Bmx tyrosine kinase induces activation of the Stat signaling pathway, which is specifically inhibited by protein kinase Cδ. ***Blood*** 11: 4341-4353, 1997.

173. Klefström, J., Arighi, E., Littlewood, T., Jäättelä, M., Saksela, E., Evan G.I. and Alitalo, K.: Induction of TNF-sensitive cellular phenotype by c-Myc involves p53 and impaired NF-kB activation. ***EMBO J.*** 16: 7382-7392, 1997.

174. Loughna, S., Hardman, P., Landels, E., Jussila, L., Alitalo, K. and Woolf, A.S.: A molecular and genetic analysis of renal glomerular capillary development. ***Angiogenesis*** 1: 84-101, 1997.

175. Achen, M.G., Jeltsch, M., Kukk, E., Mäkinen, T., Vitali, A., Wilks, A.F., Alitalo, K. and Stacker, S.A.: Vascular endothelial growth factor D (VEGF-D) is a ligand for the tyrosine kinases VEGF receptor-2 (Flk1) and VEGF receptor 3 (Flt4). ***Proc. Natl. Acad. Sci*** 95: 548-553, 1998.

176. Joukov, V., Kumar, V., Sorsa, T., Arighi, E., Weich, H., Saksela, O. and Alitalo, K.: A recombinant mutant vascular endothelial growth factor-C that has lost vascular endothelial growth factor receptor-2 binding, activation and vascular permeability activities. ***J. Biol. Chem.*** 273: 6599-6602, 1998.

177. Ristimäki, A., Narko, K., Enholm, B., Joukov, V. and Alitalo, K.: Proinflammatory cytokines regulate expression of the lymphatic endothelial mitogen vascular endothelial growth factor-C. ***J. Biol. Chem.*** 273: 8413-8418, 1998.

178. Jussila, L., Valtola, R., Partanen, T., Salvén, P., Heikkilä, P., Matikainen, M.-T., Renkonen, R., Kaipainen, A., Detmar, M., Tschachler, E., Alitalo, R. and Alitalo, K.: Lymphatic endothelium and Kaposi's sarcoma spindle cells detected by antibodies against the vascular endothelial growth factor receptor-3. ***Cancer Res.*** 58: 1599-1604, 1998.

179. Eichmann, A., Corbel, C., Jaffredo, T., Bréant, C., Joukov, V., Kumar, V., Alitalo, K. and le Douarin, N. M.: Avian VEGF-C: cloning, embryonic expression pattern and stimulation of the differentiation of VEGFR2-expressing endothelial cell precursors. ***Development*** 125: 743-752, 1998.

180. Kinnula, V.L., Aito, H., Alitalo, K., Klefstrom, J. and Raivio, K.O.: Similarities between TNF and exogenous oxidants on the cytotoxic response of c-Myc-expressing fibroblasts in vitro. ***Cancer Letters*** 125: 191-198, 1998.

181. Gaudenz, K., Roessler, E., Vainikka, S., Alitalo, K. and Muenke, M.: Analysis of patients with various craniosynostosis syndromes for a Pro24Arg mutation in FGFR4. ***Mol. Genet. Metab.*** 64: 76-79, 1998.

182. Wartiovaara, U., Salvén, P., Mikkola, H., Lassila, R., Kaukonen, J., Joukov, V., Orpana, A., Ristimäki, A., Heikinheimo, M., Joensuu, H., Alitalo, K. and Palotie, A.: Peripheral blood platelets express VEGF-C and VEGF which are released during platelet activation. ***Thromb. Haemost.*** 80: 171-175, 1998.

183. Salven, P., Lymboussaki, A., Heikkilä, P., Jääskelä-Saari, H., Enholm, B., Aase, K., von Euler, G., Eriksson, U., Alitalo, K. and Joensuu, H.: Vascular endothelial growth factors VEGF-B and VEGF-C are expressed in human tumors. ***Am. J. Pathol.*** 153: 103-108, 1998.

184. Lymboussaki, A., Partanen, T., Olofsson, B., Thomas-Crusells, J., Fletcher, C.D.M., de Waal, R.M.W., Kaipainen, A. and Alitalo, K.: Expression of the vascular endothelial growth factor C receptor VEGFR-3 in lymphatic endothelium of the skin and in vascular tumors. ***Am. J. Pathol.*** 153: 395-403, 1998.

185. Kim, J.-O., Nau, M.M., Allikian, K.A., Mäkelä, T.P., Alitalo, K., Johnson, B.E. and Kelley, M.J.: Co-amplification of a novel cyclophilin-like gene (*PPIE*) with L-*myc* in small cell lung cancer cell lines. ***Oncogene*** 17: 1019-1026, 1998.

186. Vuorela, P., Matikainen, M.-T., Kuusela, P., Ylikorkala, O., Alitalo, K. and Halmesmäki, E.: Endothelial Tie receptor antigen in maternal and cord blood of healthy and preeclamptic subjects. ***Obstet. & Gynecol.*** 92: 179-182, 1998.

187. Pepper, M. S., Mandriota, S. J., Jeltsch, M., Kumar, V. and Alitalo, K.: Vascular endothelial growth factor (VEGF)-C synergizes with basic fibroblast growth factor and VEGF in the induction of angiogenesis in vitro and alters endothelial cell extracellular proteolytic activity. ***J. Cell Physiol.*** 177: 439-452, 1998.

188. Olofsson, B., Korpelainen, E., Pepper, M. S., Mandriota, S., Aase, K., Kumar, V., Gunji, Y., Jeltsch, M., Shibuya, M., Alitalo, K. and Eriksson, U.: Vascular endothelial growth factor B (VEGF-B) binds to VEGF receptor-1 and regulates plasminogen activator activity in endothelial cells. ***Proc. Natl. Acad. Sci.*** 95: 11709-11714, 1998.

189. Cao, Y., Linden, P., Farnebo, J., Cao, R., Eriksson, A., Kumar, V., Qi, J.-H., Claesson-Welsh, L., Alitalo, K.: Vascular endothelial growth factor-C induces angiogenesis *in vivo*. ***Proc. Natl. Acad. Sci.*** 95: 14389-14394, 1998.

190. Dumont, D.J., Jussila, L., Taipale, J., Lymboussaki, A., Mustonen, T., Pajusola, K., Breitman, M. and Alitalo, K. Cardiovascular failure in mouse embryos deficient in VEGF receptor-3. ***Science*** 282: 946-949, 1998.

191. Korpelainen, E.I., Karkkainen, M.J., Tenhunen, A., Lakso, M., Rauvala, H., Vierula, M., Parvinen, M. and Alitalo, K.: Overexpression of VEGF in testis and epididymis causes infertility in transgenic mice: Evidence for nonendothelial targets for VEGF. ***J. Cell Biol.*** 143: 1705-1712, 1998.

192. Vuorela-Vepsäläinen, P., Alfthan, H., Orpana, A., Alitalo, K., Stenman, U.-H. and Halmesmäki, E.: Vascular endothelial growth factor is bound in amniotic fluid and maternal serum. ***Human Reprod.*** 14: 1346-1351, 1998.

293. Ruohola, J., Valve, E., Kärkkäinen, M., Joukov, V., Alitalo, K. and Härkönen, P.: Vascular Endothelial Growth Factors Are Differentially Regulated by Steroid Hormones and Antiestrogens in Breast Cancer Cells. ***Mol. Cell. Endocrinol.*** 149: 29-40, 1999.

194. Breiteneder-Geleff, S., Soleiman, A., Kowalski, H., Horvat, R., Amann, G., Kriehuber, E., Diem, K., Weniger, W., Tschachler, E., Alitalo, K. and Kerjaschki, D.: Angiosarcomas express mixed endothelial phenotypes of blood and lymphatic capillaries: podoplanin as a specific marker for lymphatic endothelium. ***Am. J. Pathol.*** 154: 385-394, 1999.

195. Weninger, W., Partanen, T. A., Breiteneder-Geleff, S., Mayer, C., Kowalski, H., Mildner, M, Pammer, J., Stürzl, M., Kerjaschki, D., Alitalo, K. and Tschachler, E.: Expression of vascular endothelial growth factor receptor-3 and podoplanin suggests a lymphatic endothelial cell origin of Kaposi's sarcoma tumor cells. ***Lab. Invest.*** 79: 243-251, 1999.

196. Valtola, R., Salven, P., Heikkilä, P., Taipale, J., Joensuu, H., Rehn, M., Pihlajaniemi, T., Weich, H., deWaal, R. and Alitalo, K.: VEGFR-3 and its ligand VEGF-C are associated with angiogenesis in breast cancer. ***Am. J. Pathol.*** 154: 1381-1390, 1999.

197. Partanen, T., Mäkinen, T., Arola, J., Suda, T., Weich, H. and Alitalo, K.: Endothelial growth factor receptors in human fetal heart. ***Circulation*** 100: 583-586, 1999.

198. Mäkinen, T., Olofsson, B., Karpanen, T., Hellman, U., Soker, S., Klagsbrun, M., Eriksson, U. and Alitalo, K.: Differential binding of vascular endothelial growth factor B splice and proteolytic isoforms to Neuropilin-1. ***J. Biol. Chem.*** 274: 21217-21222, 1999.

199. Aase, K., Lymboussaki, A., Kaipainen, A., Olofsson, B., Alitalo, K. and Eriksson, U.: The localization of VEGF-B in the mouse embryo suggests a paracrine role of the growth factor in the developing vasculature in vitro. ***Dev. Dynamics*** 215: 12-25, 1999.

200. Marchio, S., Primo, L., Pagano, M., Palestro, G., Albini, A., Veikkola, T., Cascone, I., Alitalo, K. and Bussolino, F.: Vascular endothelial growth factor-C stimulates the migration and proliferation of Kaposi's sarcoma cells. *J. Biol. Chem.* 274: 27617-27622, 1999.

201. Stacker, S.A., Stenvers, K., Caesar, C., Vitali, A., Domagala, T., Nice, E., Roufail, S., Simpson, R.J., Moritz, R., Karpanen, T., Alitalo, K. and Achen, M.G.: Biosynthesis of vascular endothelial growth factor-D involves proteolytic processing which generates non-covalent homodimers. *J. Biol. Chem.* 45: 32127-32136, 1999.

202. Partanen, T., Alitalo, K. and Miettinen, M.: Lack of lymphatic vascular specificity of VEGFR-3: A novel marker for human vascular tumors. *Cancer* 86:2406-2412, 1999.

203. Lymboussaki, A., Olofsson, B., Eriksson, U. and Alitalo, K.: Vascular endothelial growth factor (VEGF) and VEGF-C show overlapping binding sites in embryonic endothelia and distinct sites in differentiated adult endothelia. *Circulation Res.* 85: 992-999, 1999.

204. Iljin, K., Dube, A., Kontusaari, S., Korhonen, J., Lahtinen, I., Oettgen, P.and Alitalo, K.: Role of Ets factors in the activity and endothelial cell specificity of the mouse Tie gene promoter. *FASEB J.* 13: 377-386, 1999.

205. Korpelainen, E. I., Kärkkäinen, M., Gunji, Y., Vikkula, M. and Alitalo, K.: Endothelial receptor tyrosine kinases activate the STAT signaling pathway: mutant Tie-2 causing venous malformations signals a distinct STAT activation response. *Oncogene* 18: 1-8, 1999.

206. Wise, L.M., Veikkola, T., Mercer, A.A., Savory, L.J., Mäkinen, T., Fleming, S.B., Caesar, C., Vitali, A., Mäkinen, T., Alitalo, K. and Stacker, S.A.: Vascular endothelial growth factor (VEGF) -like protein from orf virus NZ2 binds to VEGFR2 and Neuropilin-1. *Proc. Natl. Acad. Sci.* 96: 3071-3076, 1999.

207. Klefstrom, J., Kovanen, P.E., Somersalo, K., Hueber, A-O., Littlewood, T., Evan, G., Greenberg, A., Saksela, E., Timonen, T. and Alitalo, K.: c-Myc and E1A induced cellular sensitivity to activated NK cells involves cytotoxic granules as death effectors. *Oncogene* 18: 2181-2188, 1999.

208. Dupin, N., Fisher, C., Kellam, P., Ariad, S., Tulliez, M., Franck, N., Van Mark, E., Salmon, D., Gorin, I., Escande, J.-P., Weiss, R.A., Alitalo, K. and Boshoff, C.: Distribution of human herpervirus-8 latently infected cells in Kaposi's sarcoma, multicentric Castelman's disease, and primary effusion lymphoma. *Proc. Natl. Acad. Sci.* 96: 4546-4551, 1999.

Reviews:

1. Vaheri, A., Alitalo, K., Hedman, K., Keski-Oja, J., Kurkinen, M. and Wartiovaara, J.: Fibronectin and the pericellular matrix of normal and transformed adherent cells. *Ann. N.Y. Acad. Sci.* 312: 343-353, 1978.

2. Alitalo, K.: Connective tissue glycoproteins of normal differentiated and of malignant human cells. *Academic Dissertation,* University of Helsinki, Helsinki, Finland, 1980.

3. Vaheri, A., Alitalo, K., Hedman, K., Kurkinen, M., Saksela, O. and Vartio, T.: Fibronectin and its loss in malignant transformation. In: *Biochemistry of Normal and Pathological Connective Tissue.* Colloc. Intern. du C.N.R.S. 287: 249-254, 1980.

4. Kurkinen, M., Alitalo, K., Hedman, K. and Vaheri, A.: Fibronectin, procollagen and the pericellular matrix in normal and tranformed fibroblast cultures. In: *Biology of Collagen* (A. Viidik & J. Vuust, eds.), pp. 223-235. Academic Press, New York, 1980.

5. Vaheri, A., Vartio, T., Stenman, S., Saksela, O., Hedman, K. and Alitalo, K.: Fibronectin and proteinases in tumor invasion. In: *Proteinases and Tumor Invasion* (P. Sträuli, A.J. Barrett & A. Baici, eds.), pp. 49-57. Raven Press, New York, 1980.

6. Vaheri, A., Keski-Oja, J., Vartio, T., Alitalo, K., Hedman, K. and Kurkinen, M.: Structure and functions of fibronectin. In: *Gene Families of Collagen and of Other Proteins* (D.J. Prockop & P.C. Champe, eds.), Elsevier/North-Holland, New York, Developments of Biochemistry 15: 161-178, 1980.

7. Vaheri, A. and Alitalo, K.: Pericellular matrix glycoproteins in cell differentiation and in malignant transformation. In: *Cellular Controls in Differentiation* (D. Rees & C. Lloyd, eds.), pp. 29-56. Academic Press. New York, 1981.

8. Alitalo, K. and Vaheri, A.: Pericellular matrix in malignant transformation. *Adv. Cancer Res.* 37: 111-158, 1982.

9. Vaheri, A., Alitalo, K., Hedman, K., Keski-Oja, J. and Vartio, T.: Fibronectin and epithelial cells. In: ***Structural Carbohydrates of the Liver***, Falk Symposium No 34: 385-398. MTP Press, Lancaster, 1983.

10. Alitalo, K.: Amplification of cellular oncogenes in cancer cells (a review). ***Med. Biol.*** 62: 304-317, 1984.

11. Alitalo, K., Saksela, K., Winqvist, R., Schwab, M. and Bishop, J.M.: Amplification and aberrant expression of cellular oncogenes in human colon cancer cells. In: ***Genes and Cancer*** (J.M. Bishop, M. Graves & J. Rowley, eds.). Alan Liss Inc., New York, pp. 383-397, 1984.

12. Schwab, M., Alitalo, K., Varmus, H.E. and Bishop, J.M.: Amplification of cellular oncogenes in tumor cells. In: ***The Cancer Cells***, (G.F. Vande Woude, A.J. Levine, W.C. Topp & J.D. Watson, eds.). Cold Spring Harbor Press, p. 215-220, 1984.

13. Alitalo, K.: Amplification of cellular oncogenes in tumor cells. ***Trends Biochem. Sci.*** 10: 194-197, 1985.

14. Alitalo, K., Keski-Oja, J., Saksela, K. and Winqvist, R.: Amplification of cellular oncogenes in colon and lung cancer cells. In: ***Retroviruses and Human Pathology***, (R.C. Gallo, D. Stehelin & O.E. Varnier, eds.). Humana Press, New York, pp. 485-495, 1985.

15. Oker-Blom, N., Pfeifer-Ohlsson, S., and Alitalo, K: Retroviruses in neoplasia yesterday, today and tomorrow. In: ***Retroviruses and Human Pathology***, (R.C. Gallo, D. Stehelin, & O.E. Varnier, eds.), Humana Press, New York, pp. 1-18, 1985.

16. Alitalo, K. and Schwab, M.: Oncogene amplification in tumor cells. ***Adv. Cancer Res.*** 47: 235-281, 1985.

17. Alitalo, K., Partanen, P., and Vaheri, A. (eds.): ***Synthetic peptides in biology and medicine.*** Elsevier Science Publ. 1985.

18. Keski-Oja, J., Alitalo, K., Barlati, S. and Vaheri, A.: Pericellular matrix in fibroblastic and epithelial cells induced by oncogenic transformation. In: ***Theories and models in cellular transformation*** (L. Santi & L. Zardi, eds.), Academic Press, London, pp. 55-70, 1985.

19. Pohjanpelto, P., Hölttä, E., Jänne, O. and Alitalo, K.: Amplification of ornithine decarboxylase gene in response to polyamine deprivation in CHO cells. In: ***Recent progress in polyamine research*** (L. Selmeci, M.E. Brosnan, & N. Seiler, eds.), VNU, The Netherlands, pp. 33-47, 1985.

20. Mäkelä, T. and Alitalo, K.: Tyrosine kinases in control of cell growth and transformation. ***Med. Biol.*** 64: 325-330, 1986.

21. Mäkelä, T.P. and Alitalo, K.: Proto-oncogene amplification: role in tumor progression. In: ***Recombinant DNA in Clinical Medicine***, Ann. Clin. Res. 18: 290-296, 1986.

22. Sistonen, L. and Alitalo, K.: Activation of c-*ras* oncogenes by mutations and amplification. In: ***Recombinant DNA in Clinical Medicine***, Ann. Clin. Res. 18: 297-303, 1986.

23. Alitalo, K., Koskinen, P., Mäkelä, T., Saksela, K., Sistonen, L. and Winqvist, R.: *myc*-oncogenes: activation and amplification. ***Biochem. Biophys. Acta Reviews on Cancer*** 907: 1-32, 1987.

24. Alitalo, K.: Amplification of cellular oncogenes in cancer cells. In: ***Oncogenes and growth factors*** (Bradshaw, R. & Prentis, S., eds.). p. 17-23, Elsevier Publications (Cambridge), 1987.)

25. Alitalo, R., Mäkelä, T.P., Alitalo, K., Betsholtz, C. and Andersson, L.C.: PDGF-gene expression in TPA-induced K562, HL-60 and U937 leukemia cells.
In: ***Recent Advances in Leukemia and Lymphoma*** (Gale R.P. & Golde D., eds.), pp. 53-61 Alan R. Liss Inc., N.Y., 1987.

26 Lohi, J., Pertovaara, L., Sistonen, L., Alitalo, K. and Keski-Oja, J.: Regulation by TGFß of genes involved in growth control. ***Ann. N. Y. Acad. Sci.*** 593: 318-320, 1990.

27. Mäkelä, T., Koskinen, P., Saksela, K. and Alitalo, K.: Biochemistry and function of *myc* oncoproteins analysed with recombinant constructs. In: ***Recombinant systems in protein expression*** (Alitalo, K., Huhtala, M.-L., Knowles, J. & Vaheri. A., eds.). Elsevier Science Publishers, Amsterdam, The Netherlands, pp. 137-144, 1990.

28. Alitalo, K., Huhtala, M.-L., Knowles, J. and Vaheri. A., editors: ***Recombinant systems in protein expression***. Elsevier Science Publishers, Amsterdam, The Netherlands, 1990.

29. Salvèn, P. and Alitalo, K.: Genes protecting from cancer (Editorial). ***Ann. Med.*** 22: 143-144, 1990.

30. Saksela, K, Koskinen, P., Hirvonen, H, Lehväslaiho, H., Mäkelä, T. and Alitalo, K.: *myc* and *neu* oncogene amplification, overexpression and protein products in human cancer. In: ***Growth Regulation and Carcinogenesis*** (W.R. Paukovits, ed.), Vol. I, pp.153-174, 1991.

31. Korhonen, J., Partanen, J., Eerola, E., Vainikka, S., Ilvesmäki, V., Voutilainen, R., Julkunen, M., Mäkelä, T. and Alitalo, K.: Novel human FGF receptors with distinct expression patterns. In: The Fibroblast Growth Factor Family (A. Baird & M. Klagsbrun, eds.). ***Ann. N. Y. Acad. Sci.*** 638:403-405, 1991.

32. Mäkelä, T.P., Mattson, K. and Alitalo, K.: Tumor markers and oncogenes in lung cancer. ***Eur. J. Cancer*** 27: 1323-1327, 1991.

33. Lehtola, L., Lehväslaiho, H., Koskinen, P. and Alitalo, K.: A chimeric EGFR/*neu* receptor in studies of *neu* function. In ***Genes, Oncogenes, and Hormones: Advances in Cellular and Molecular Biology in Breast Cancer*** (eds. R.B. Dickson and M.E. Lippman), Kluwer Academic Publishers, pp. 213-228. 1991.

34. Salven, P., Schwab, M. and Alitalo, K.: Oncogene amplification in human cancer. ***Encyclopedia of Human Cancer*** 5: 545-550, 1991.

35. Korhonen, J., Partanen, J., Eerola, E., Vainikka, S., Alitalo, R., Mäkelä, T., Sandberg, M., Hirvonen, H. and Alitalo, K: Five FGF receptors with distinct expression patterns. In: ***Angiogenesis*** (R. Steiner, P.B. Weisz & R. Langer, eds.), Academic Press, 1992, pp 91-100.

36. Partanen, J., Vainikka, S., Korhonen, J. and Alitalo, K.:Diverse receptors for fibroblast growth factors. ***Progr. Growth Factor Res.*** 4: 69-83, 1992.

37. Lehtola, L., Lehväslaiho, H., Koskinen, P. and Alitalo, K.: A chimeric EGFR/*neu* receptor in functional analysis of the *neu* oncoprotein. ***Acta Oncol.*** 31: 147-150, 1992.

38. Mäkelä, T.P., Saksela, K. and Alitalo, K.: Amplification and rearrangement of L-*myc* in human small-cell lung cancer. ***Mutat. Res.*** 276: 307-315, 1992.

39. Alitalo, K., Mäkelä, T., Saksela, K., Hirvonen, H. and Koskinen, P.: Oncogene Amplification: Analysis of *myc* Oncoproteins. In ***Gene amplification in mammalian cells: Techniques and Applications*** (ed. R. Hellems), Marcel Dekker, Inc., pp. 371-382, 1992.

40. Västrik, I., Mäkelä, T.P., Koskinen, P. and Alitalo, K.: *myc, max*, and a novel *rlf*-L-*myc* fusion protein in small cell lung cancer. In: ***Multistage Carcinogenesis***: (eds. C.C. Harris et al.), pp. 307-318, 1992.

41. Alitalo, K.: Molecular analysis of nuclear oncoproteins and receptor tyrosine kinases. In ***Academia Scientiarum Fennica:*** Year Book, pp. 187-189, 1992.

42. Koskinen, P. and Alitalo, K.: Role of *myc* amplification and overexpression in cell growth, differentiation and death. ***Semin. Cancer Biol.*** 4: 3-12, 1993.

43. Alitalo, K.: Introduction: Oncogene amplification. ***Semin. Cancer Biol.*** 4: 1. 1993.

44. Koskinen, P., Mäkelä, T.P., Västrik, I. and Alitalo, K.: *myc* Amplification: regulation of Myc function. ***Clin. Chim. Acta,*** 217: 57-62, 1993.

45. Partanen, J., Vainikka, S. and Alitalo, K.: Structural and functional specificity of FGF receptors. In: ***Phil. Trans. R. Soc. Lond.***, Series B 340: 297-303, 1993.

46. Alitalo, K., Mäkelä, T.P., Saksela, K., Koskinen, P.J. and Hirvonen, H.: Oncogene Amplification: Analysis of myc oncoproteins. In: ***Gene Amplification in Mammamlian Cells*** (Ed. R.E. Hellems). Marcel Dekker, Inc., pp. 371-382, 1993.

47. Västrik, I., Mäkelä, T.P., Koskinen, P.J., Klefström, J. and Alitalo, K.: *Myc* protein, partners and antagonists. ***Crit. Rev. Oncogenesis*** 5: 59-68, 1994.

48. Partanen, J., Lahtinen, I. and Alitalo, K.: Tie protein-tyrosine kinase. In: ***The Protein Kinase Factsbook*** (eds. D.G.Hardie and S. Hanks), Academic Press, 1995, pp. 152-153.

49. Pajusola, K., Kaipainen A. and Alitalo, K.: Flt-4 receptor PTK. In: ***The Protein Kinase Factsbook*** (eds. D.G. Hardie and S. Hanks), Academic Press, 1995, pp. 168-169.

50. Vainikka S., Mustonen T. and Alitalo K.: Fibroblast growth factors. In: ***Guidebook to Cytokines and their receptors.*** (N.A. Nicola, ed.) Oxford University Press 1995, pp 214-218.

51. Mustonen, T. and Alitalo, K.: Endothelial receptor tyrosine kinases involved in angiogenesis. ***J. Cell Biol.*** 129: 895-898, 1995.

52. Klefström, J., Saksela, E. and Alitalo, K.: Molecular mechanisms controlling susceptibility to tumor necrosis factor induced cell death. In: *Tumor Biology* Regulation of Cell Growth, Differentiation and Genetics in Cancer (Eds. Asterios S. Tsiftsoglou et al.), NATO ASI Series, Series H: Cell Biology, Vol 99, Springer Verlag pp.143-154, 1996.

53. Joukov, V., Kaipainen, A., Jeltsch, M., Pajusola, K., Olofsson, B., Kumar, V., Eriksson, U. and Alitalo, K.: Vascular endothelial growth factors VEGF-B and VEGF-C. ***J. Cell Physiol.*** 173: 211-215, 1997.

54. Böhling, T., Hatva, E., Plate, K.H., Haltia, M. and Alitalo, K.: Von Hippel-Lindau disease and capillary haemangioblastoma. In: ***Pathology & Genetics. Tumours of the Nervosus System***, (Eds. Kleihues, P. and Cawenee, W.K.), International Agency for Research on Cancer, WHO, chapter 14, pp. 179-181, 1997.

55. Korpelainen, E. and Alitalo, K.: Signaling angiogenesis and lymphangiogenesis. ***Current Opinion in Cell Biology*** 10: 159-164, 1998.

56. Enholm, B., Jussila, L., Kärkkäinen, M. and Alitalo, K.: Vascular endothelial growth factor-C, a growth factor for lymphatic endothelial cells. ***Trends in Cardiovascular Med.*** Vol. 8, No. 7, 292-297, 1998.

57. Laurén, J., Gunji, Y. and Alitalo, K:: Is angiopoietin-2 necessary for the initiation of tumor angiogenesis? ***Am. J. Pathol.*** 153: 1333-1339, 1998.

58. Taipale, J., Makinen, T., Arighi, E., Kukk, E. and Alitalo, K.: Vascular endothelial growth factor receptor-3. In: ***Curr. Topics Microbiol. Immunol.***. (Ed. Lena Claesson-Welsh), 237: 85-96, 1999.

59. Eriksson, U. and Alitalo, K.: Structure, expression and reseptor-binding properties of novel vascular endothelial growth factors. In: ***Current Topics in Microbiology and Immunology***. (Ed. Lena Claesson-Welsh), Springer Verlag, GmbH & Co, KG 237: 41-57, 1999.

60. Veikkola, T. and Alitalo, K.: VEGFs, receptors and angiogenesis. ***Semin. Cancer Biol.*** 9: 211-220, 1999.

61. Olofsson, B., Jeltsch, M., Eriksson, U. and Alitalo, K.: Current biology of VEGF B and VEGF-C. ***Pharmaceutical Biotechnology*** 10:528-535, 1999.

62. Petrova, T.V., Makinen, T., Alitalo, K.: Signaling via vascular endothelial growth factor receptors. ***Exp. Cell Res.*** 253:117-130, 1999.

63. Kaipainen, A., Kukk, E., Enholm, B., Hietanen, K., Gunji, Y. and Alitalo, K.: III Angiogenic Factors: Tie receptors, Ang ligands. In: ***Tumor Angiogenesis and Microcirculation***. (Eds. D'Amore P., Voest E., Noren T., Casella C.), Marcel Dekker, Inc., in press.

64. Kaipainen, A., Korpelainen, E., Karkkainen, M., Veikkola, T. and Alitalo, K.: Vascular endothelial growth factor receptors. In: ***Tumor Angiogenesis and Microcirculation***. (Eds. D'Amore P., Voest E., Noren T., Casella C.), Marcel Dekker, Inc., in press.

65. Alitalo, K., Gunji, Y., Alitalo, R. and Eichmann, A.: VEGF receptors in vascular development and hematopoiesis. In: ***Developmental Biology of Hematopoiesis***. (Ed. Leonard I. Zon), in press.

66. Veikkola, T., Karkkainen, M., Claesson-Welsh, L. and Alitalo, K.: Regulation of Angiogenesis via Vascular Endothelial Growth Factor Receptors. ***Cancer Res.***, in press.

67. Ferrara, N. and Alitalo, K.: Clinical applications of angiogenic growth factors and their inhibitors. *Nature Med.* 5: 1359-1364, 1999.

Publications in Finnish:

1. Alitalo, K., Saksela, O. and Vaheri, A.: Sidekudos ja maligni solu (Connective tissue and malignant cells, a review in Finnish). *Duodecim* 96: 1572-1783, 1980.

2. Vaheri, A. and Alitalo, K.: Retrovirukset ja ihmisen syöpägeenit (Retroviruses and human oncogenes). *Duodecim* 99: 452-457, 1983.

3. Alitalo, K., and Vaheri, A.: Syöpägeenit (Oncogenes). *Duodecim* 99: 1383-1399, 1983.

4. Keski-Oja, J. and Alitalo, K.: Verihiutalekasvutekijä (PDGF) - onkogeenin tuote. (Platelet-derived growth factor - product of an oncogene). *Duodecim* 99: 1243-1246, 1983.

5. Alitalo, K. and Vaheri, A.: Syövän synty geeneissä. (The origin of cancer in genes). *Tiede 2000* (Science 2000) 9: 50-55, 1983.

6. Alitalo, K. and Keski-Oja, J.: Erytroblastoosionkogeeni on osa kasvutekijäreseptorin geeniä. (Erythroblastosis oncogene - part of a growth factor gene). *Duodecim* 100: 460-461, 1984.

7. Alitalo, K.: Syöpägeenit. (Oncogenes). In: *"Syövän Biologia"* (Cancer Biology) (K. Alitalo, L. Andersson, L. Teppo, & A. Vaheri, eds.) pp. 103-115, WSOY, 1985.

8. Alitalo, K. and Vaheri, A.: Syöpäsolun ilmiasu (The phenotype of cancer cells). In: *Syövän Biologia* (Cancer Biology) (K. Alitalo, L. Andersson, L. Teppo & A. Vaheri, eds.) pp. 157-172, WSOY, 1985.

9. Vaheri, A., and Alitalo, K.: Virukset syövän aiheuttajina (Viruses as causes of cancer) In: *Syövän Biologia* (Cancer Biology) (K. Alitalo, L. Andersson, L. Teppo, & A. Vaheri, pp. 135-144, WSOY, 1985.

10. Alitalo, K., Andersson, K., Teppo, L., and Vaheri, A. (eds.). *Syövän Biologia* (Cancer Biology) WSOY, 1985.

11. Aho, M., Alitalo, K. and Syrjänen, K.: Syylistä syöpään. (From Papilloma to Carcinoma. An editorial in Finnish). *Suomen Lääkärilehti* (The Finnish Medical Journal) 24: 2242, 1985.

12. Alitalo, K. and Keski-Oja, J.: Uusi autokriininen syövän syntymekanismi (A novel autocrine mechanism of tumorigenesis). *Duodecim* 101: 1543-1546, 1985.

13. Keski-Oja, J., Laiho, M. and Alitalo, K.: Kasvutekijät ja syöpä. (Growth factors and cancer) *Tiede 2000* (Science 2000) 1: 18-21, 1986.

14. Saksela, K., Mäkelä, T. and Alitalo, K.: Keuhkosyövän molekyylibiologiaa. (On the molecular biology of lung cancer). *Suomen Lääkärilehti* (The Finnish Medical Journal) 18: 1712-1718, 1986.

15. Alitalo, K.: Syöpägeenit. (Oncogenes). *Otavan Suuri Ensyklopedia* 9842-9844, 1986.

16. Keski-Oja, J. and Alitalo, K.: Transformoiva kasvutekijä-ß ja maligni kasvu. (Transforming growth factorß and malignant growth). *Duodecim* 102: 1015-1023, 1986.

17. Saksela, O. and Alitalo, K.: Angiogeeninen onkogeeni. (An angiogenic oncogene). *Duodecim* 104: 67, 1987.

18. Lehtola, L. and Alitalo, K.: Onkogeenien kliininen merkitys. (The clinical significance of oncogenes). *Duodecim* 104: 1847-1863, 1988.

19. Winqvist, R., Krusius, T. and Alitalo, K.: Syöpälääkeresistenssin molekulaariset mekanismit. (The molecular mechanisms of drug resistance). *Duodecim* 105: 1707-1714, 1989.

20. Alitalo, K.: Lääketieteen Nobelin palkinto soluonkogeenien löytäjille. (The discoverers of cellular oncogenes receive the Nobel Prize). *Duodecim* 105: 1887-1891, 1989.

Saksela, K. and Alitalo, K.: Mitä onkogeenit ovat ja miksi niitä tutkitaan? (What are oncogenes and why are they being studied).

Suomen Lääkärilehti (The Finnish Medical Journal) 44: 1567-1570, 1989.

22. Lehtonen, E. and Alitalo, K.: A course on transgenic mice. ***Opetusmoniste*** Helsinki University Press, 1989.

23. Lehväslaiho, H., Mäkelä, T. and Alitalo, K.: Proto-onkogeenit ja solujen kasvun säätely. (Proto-oncogenes and cell growth control). *Duodecim* 106: 261-277, 1990.

24. Alitalo., K. and Petterson, R: Geenien kohdennettu muuntelu - perustutkimuksen uusin täsmäase. (Targeted mutagenesis - a new tool of basic research). *Duodecim* 106: 343-346, 1990.

25. Markkula, M., Alitalo, K. and Lehtonen, E.: Geeni siirtyy, tieto kasvaa. (Gene transfer - for growth of knowledge). *Tiede 2000* (Science 2000) 4: 46-49, 1990.

26. Alitalo, K: Lääketieteen ja fysiologian Nobelin palkinto molekyylibiologiselle syöpätutkimukselle. (The Nobel Prize in medicine for molecular cancer research). *Kemia-Kemi* 17: 226-230, 1990.

27. Alitalo, K.: Molekyylitutkimus iskee ytimeen. (Molecular biology hits the bone marrow). *Duodecim* 106: 1631-1632, 1990.

28. Alitalo, K.: Katala perintö. (A bad inheritance). *Duodecim* 107: 132-133, 1991.

29. Korhonen J., Eerola E. and Alitalo K.: Onkogeenit ja tuumorisupressorigeenit solun kasvun säätelijöinä. (Oncogenes and tumor suppressor genes as regulators of cell growth) ***Solubiologi*** 2: 127-134, 1991.

30. Lehtola, L. ja Alitalo, K.: Rintasyövän ennusteen arviointi. (Prognosis of breast cancer) *Duodecim* 107: 903-905, 1991.

31. Laiho, M. ja Alitalo, K.: Kasvurajoitegeenien muutokset syövän syntymekanismina. (Suppressor genes in tumorigenesis) *Duodecim* 107: 1680-1691, 1991.

32. Klefström, J., Saksela, E. and Alitalo, K.: Tuumorinekroositekijä ja solutapon monimutkainen laukaisumekanismi. (Tumor necrosis factor and the complicated triggering of cell death) *Duodecim* 108: 1449-1455, 1992.

33. Paloheimo, M., Saksela, O., Pyrhönen, S. and Alitalo, K.: Melanooman kasvun säätely. (Growth control in melanomas) *Duodecim* 108: 2097-2104, 1992.

34. Alitalo, K and Pettersson, R.: Syövän synnyn molekyyligeneettiset ja -biologiset mekanismit. (The molecular genetic and molecular biologic causes of cancer) *Duodecim* 109: 809-813, 1993.

35. Silvennoinen, O., Julkunen, I. ja Alitalo, K.: Interferonien kuuma linja tumaan. (Interferon hot line to the nucleus) *Duodecim* 109: 1447-1449, 1993.

36. Winqvist, R. ja Alitalo, K.: Periytyvän rintasyöpäalttiuden riskigeenit selviämässä. (Revealing breast cancer susceptibility genes) *Duodecim* 111: 113-115, 1995.

37 Alitalo, K.: Geenit ja syöpä (Genes and cancer). In: ***Tutkimuksen etulinjassa/Tieteen päivät 1995*** (Science days-1995), 225-231, 1995,WSOY.

38. Alitalo, K.: Endoteelin kasvutekijä-ja reseptorigeenit. *Duodecim* 112: 341-344, 1996.

39. Jussila, L., Alitalo, K. ja Kaipainen, A.: Uutta imua lymfasuoniston biologiaan. *Duodecim* 114: 343-348, 1998.

40. Alitalo, K.: Onkogeeneistä syövän molekyylibiologiaan ja angiogeneesin estoon (Matti Äyräpään luento) *Duodecim* 114: 2545-2553, 1998.

41. Alitalo, K.: Uusi geenitekniikka syöpätutkimuksessa. (New gene technology in cancer research) ***Geeni- ja biotekniikka***, Otava, in press.

Patents

Kari Alitalo, CV and publications

United States Patent 5,607,918 Eriksson, et. al. Mar. 4, 1997 Vascularendothelial growth factor-B and DNA coding therefor Inventors: Eriksson;Ulf (B.ang.lsta, SE); Olofsson;Birgitta (Sundbyberg, SE); Alitalo; Kari (Helsinki, FI); Pajusola; Katri (Helsinki, FI). Assignee: Ludwig Institute for Cancer Research (New York, NY); Helsinki University Licensing Ltd. Oy (University of Helsinki, FI). Appl. No.: Filed: Jun. 6, 1995

nited States Patent 5,776,755 Alitalo, et. al. Jul. 7, 1998 FLT4, a receptor tyrosine kinase Inventors: Alitalo; Kari (Espoo, FI); Aprelikova; Olga (Helsinki, FI); Pajusola; Katri (Helsinki, FI); Armstrong; Elina (Helsinki, FI); Korhonen; Jaana (Helsinki, FI); Kaipainen; Arja (Helsinki, FI). Assignee: Helsinki University Licensing, Ltd. (Helsinki, FI). Filed: Nov. 14, 1994

AUSTRALIA

Patents Act 1990

IN THE MATTER OF Australian Patent Application Serial No 696764 by Human Genome Sciences, Inc.

-and-

IN THE MATTER OF Opposition thereto by Ludwig Institute for Cancer Research

THIS IS Exhibit 2 referred to in the Statutory Declaration of Kari Alitalo made before me this 15th Day of February, 2000

OLLI-PEKKA SIRO
Notary Public
Notary Public

HELSINGIN MAISTRAATTI
MAGISTRATEN I HELSINGFORS

EXHIBIT 2

Nucleotide and Amino Acid Sequence of VEGF-C and primers to make VEGF2(HGS)

The 5' and 3' primers used in the PCR reaction are indicated in capital letters. The BamHI site in the 5' primer and the XbaI site in the 3' primer are underlined. The 3' primer also encodes an HA-tag 3' to the last codon of VEGF-C (which encodes a serine), followed by a stop codon indicated in boldface.

```
ccacccctgc ccccgccagc ggaccggtcc cccacccccg gtccttccac c atg cac  357
                                                          Met His
                                                            1

ttg ctg ggc ttc ttc tct gtg gcg tgt tct ctg ctc gcc gct gcg ctg   405
Leu Leu Gly Phe Phe Ser Val Ala Cys Ser Leu Leu Ala Ala Ala Leu
          5                  10                  15

ctc ccg ggt cct cgc gag gcg ccc gcc gcc gcc gcc gcc ttc gag tcc   453
Leu Pro Gly Pro Arg Glu Ala Pro Ala Ala Ala Ala Ala Phe Glu Ser
     20                  25                  30

gga ctc gac ctc tcg gac gcg gag ccc gac gcg ggc gag gcc acg gct   501
Gly Leu Asp Leu Ser Asp Ala Glu Pro Asp Ala Gly Glu Ala Thr Ala
 35                  40                  45                  50

tat gca agc aaa gat ctg gag gag cag tta cgg tct gtg tcc agt gta   549
Tyr Ala Ser Lys Asp Leu Glu Glu Gln Leu Arg Ser Val Ser Ser Val
                 55                  60                  65
```

5'-CGC GGA TCC ATG ACT GTA CTC TAC CCA-3' 5' Primer

```
gat gaa ctc atg act gta ctc tac cca gaa tat tgg aaa atg tac aag   597
Asp Glu Leu Met Thr Val Leu Tyr Pro Glu Tyr Trp Lys Met Tyr Lys
            70                  75                  80

tgt cag cta agg aaa gga ggc tgg caa cat aac aga gaa cag gcc aac   645
Cys Gln Leu Arg Lys Gly Gly Trp Gln His Asn Arg Glu Gln Ala Asn
          85                  90                  95

ctc aac tca agg aca gaa gag act ata aaa ttt gct gca gca cat tat   693
Leu Asn Ser Arg Thr Glu Glu Thr Ile Lys Phe Ala Ala Ala His Tyr
     100                 105                 110

aat aca gag atc ttg aaa agt att gat aat gag tgg aga aag act caa   741
Asn Thr Glu Ile Leu Lys Ser Ile Asp Asn Glu Trp Arg Lys Thr Gln
115                 120                 125                 130

tgc atg cca cgg gag gtg tgt ata gat gtg ggg aag gag ttt gga gtc   789
Cys Met Pro Arg Glu Val Cys Ile Asp Val Gly Lys Glu Phe Gly Val
                135                 140                 145

gcg aca aac acc ttc ttt aaa cct cca tgt gtg tcc gtc tac aga tgt   837
Ala Thr Asn Thr Phe Phe Lys Pro Pro Cys Val Ser Val Tyr Arg Cys
            150                 155                 160

ggg ggt tgc tgc aat agt gag ggg ctg cag tgc atg aac acc agc acg   885
Gly Gly Cys Cys Asn Ser Glu Gly Leu Gln Cys Met Asn Thr Ser Thr
          165                 170                 175

agc tac ctc agc aag acg tta ttt gaa att aca gtg cct ctc tct caa   933
Ser Tyr Leu Ser Lys Thr Leu Phe Glu Ile Thr Val Pro Leu Ser Gln
     180                 185                 190
```

```
ggc ccc aaa cca gta aca atc agt ttt gcc aat cac act tcc tgc cga   981
Gly Pro Lys Pro Val Thr Ile Ser Phe Ala Asn His Thr Ser Cys Arg
195                 200                 205                 210

tgc atg tct aaa ctg gat gtt tac aga caa gtt cat tcc att att aga  1029
Cys Met Ser Lys Leu Asp Val Tyr Arg Gln Val His Ser Ile Ile Arg
                215                 220                 225

cgt tcc ctg cca gca aca cta cca cag tgt cag gca gcg aac aag acc  1077
Arg Ser Leu Pro Ala Thr Leu Pro Gln Cys Gln Ala Ala Asn Lys Thr
            230                 235                 240

tgc ccc acc aat tac atg tgg aat aat cac atc tgc aga tgc ctg gct  1125
Cys Pro Thr Asn Tyr Met Trp Asn Asn His Ile Cys Arg Cys Leu Ala
        245                 250                 255

cag gaa gat ttt atg ttt tcc tcg gat gct gga gat gac tca aca gat  1173
Gln Glu Asp Phe Met Phe Ser Ser Asp Ala Gly Asp Asp Ser Thr Asp
    260                 265                 270

gga ttc cat gac atc tgt gga cca aac aag gag ctg gat gaa gag acc  1221
Gly Phe His Asp Ile Cys Gly Pro Asn Lys Glu Leu Asp Glu Glu Thr
275                 280                 285                 290

tgt cag tgt gtc tgc aga gcg ggg ctt cgg cct gcc agc tgt gga ccc  1269
Cys Gln Cys Val Cys Arg Ala Gly Leu Arg Pro Ala Ser Cys Gly Pro
                295                 300                 305

cac aaa gaa cta gac aga aac tca tgc cag tgt gtc tgt aaa aac aaa  1317
His Lys Glu Leu Asp Arg Asn Ser Cys Gln Cys Val Cys Lys Asn Lys
            310                 315                 320

ctc ttc ccc agc caa tgt ggg gcc aac cga gaa ttt gat gaa aac aca  1365
Leu Phe Pro Ser Gln Cys Gly Ala Asn Arg Glu Phe Asp Glu Asn Thr
        325                 330                 335

tgc cag tgt gta tgt aaa aga acc tgc ccc aga aat caa ccc cta aat  1413
Cys Gln Cys Val Cys Lys Arg Thr Cys Pro Arg Asn Gln Pro Leu Asn
    340                 345                 350

cct gga aaa tgt gcc tgt gaa tgt aca gaa agt cca cag aaa tgc ttg  1461
Pro Gly Lys Cys Ala Cys Glu Cys Thr Glu Ser Pro Gln Lys Cys Leu
355                 360                 365                 370

tta aaa gga aag aag ttc cac cac caa aca tgc agc tgt tac aga cgg  1509
Leu Lys Gly Lys Lys Phe His His Gln Thr Cys Ser Cys Tyr Arg Arg
                375                 380                 385

cca tgt acg aac cgc cag aag gct tgt gag cca gga ttt tca tat agt  1557
Pro Cys Thr Asn Arg Gln Lys Ala Cys Glu Pro Gly Phe Ser Tyr Ser
            390                 395                 400

                                    3'Primer 3' TCT GGT GTT TAC

gaa gaa gtg tgt cgt tgt gtc cct tca tat tgg aaa aga cca caa atg  1605
Glu Glu Val Cys Arg Cys Val Pro Ser Tyr Trp Lys Arg Pro Gln Met
        405                 410                 415

TCG GAG CTC ATG GGT ATG CTG CAG GGT CTG ATG CGA ACT AGA TCT CGC-5'

agc taagattgta ctgttttcca gttcatcgat tttctattat ggaaaactgt       1658
Ser
```

AUSTRALIA

Patents Act 1990

IN THE MATTER OF Australian Patent Application Serial No 696764 by Human Genome Sciences, Inc.

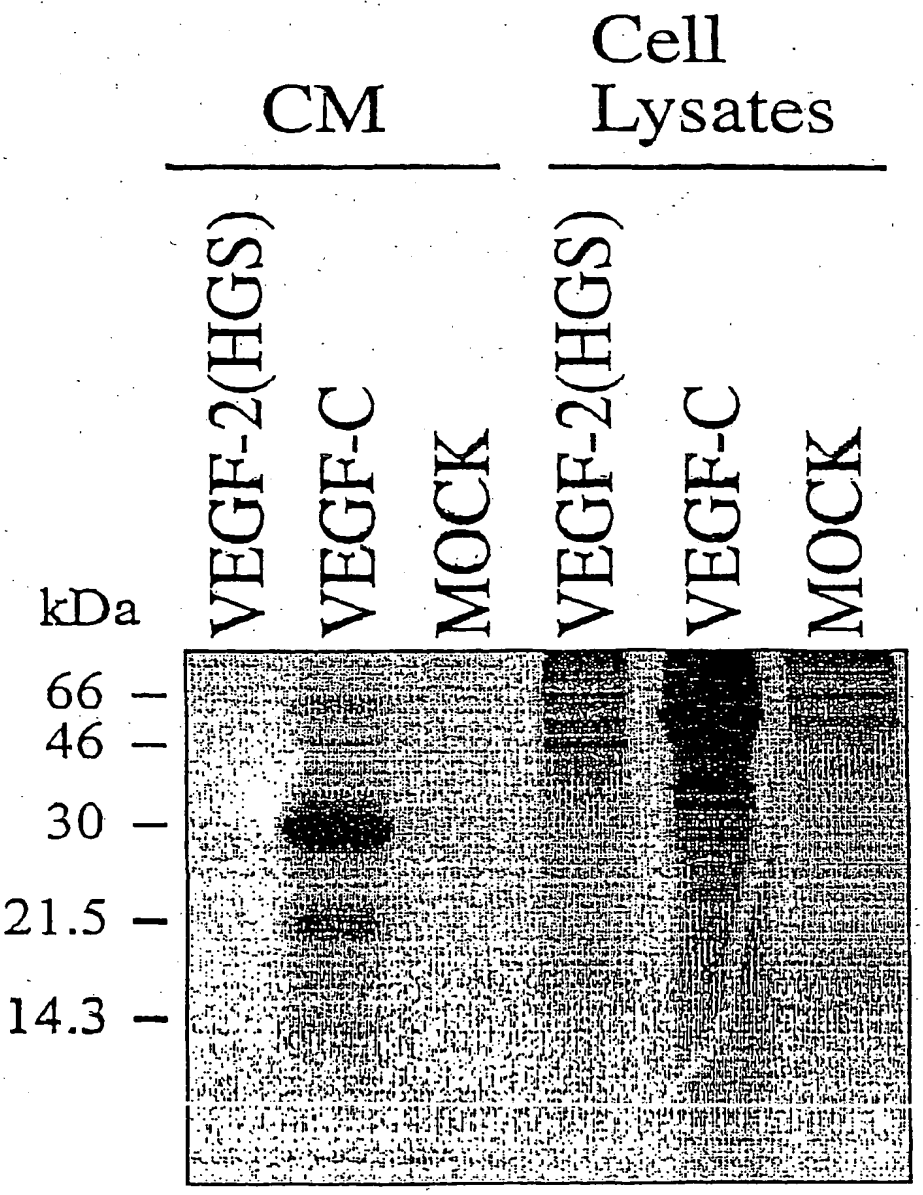
-and-

IN THE MATTER OF Opposition thereto by Ludwig Institute for Cancer Research

THIS IS Exhibit 3 referred to in the Statutory Declaration of Kari Alitalo made before me this 15th Day of February, 2000

OLLI-PEKKA SIRO
Notary Public
Notary Public

HELSINGIN MAISTRAATTI
MAGISTRATEN I HELSINGFORS


CM
Cell Lysates
VEGF-2(HGS)
VEGF-C
MOCK
VEGF-2(HGS)
VEGF-C
MOCK
kDa
66
46
30
21.5
14.3

AUSTRALIA

Patents Act 1990

IN THE MATTER OF Australian Patent Application Serial No 696764 by Human Genome Sciences, Inc.

-and-

IN THE MATTER OF Opposition thereto by Ludwig Institute of Cancer Research

STATUTORY DECLARATION

I, Francis John Ballard of 52A Bridge Street, Kensington, South Australia 5068, do solemnly and sincerely declare as follows :

1. I currently hold the positions of Managing Director, GroPep Pty Ltd, Director and Chairman of PrimeGRO Pty Ltd and Affiliate Professor in Biotechnology at the University of Adelaide. I received my BSc with Honours in 1961 and my PhD in 1964, both of which were awarded by the University of Western Australia. Since that time I have worked substantially continuously as a scientific researcher in the USA and Australia in cellular biochemistry and molecular biology, with a particular focus since approximately 1980 on the molecular biology and mechanism of action of growth factors, including research into wound healing, endothelial cell growth, and angiogenesis. In addition to my own research efforts, I was Director of the Cooperative Research Centre ("CRC") for Tissue Growth and Repair (1991 to 1999), which required me to direct and coordinate the research programs of the CRC. In recognition of my distinguished contributions to scientific research I was awarded the Lemberg Medal by the Australian Biochemical Society (now the Australian Society for Biochemistry and Molecular Biology) in 1984 and in 1997 was elected a Fellow of the Australian Academy of Technological Sciences and Engineering. I receive numerous invitations to speak at national and international symposia in the areas of my scientific expertise. I also supervise the post-graduate research of others, and have authored and co-authored numerous original research articles published in peer-reviewed journals and I have (and do) serve on the editorial board of such journals. My detailed *Curriculum Vitae* is attached hereto as Exhibit 1.

2. I have been asked by the Ludwig Institute for Cancer Research ("Ludwig Institute") to serve as a scientific expert in connection with Ludwig Institute's opposition to the issuance of a Patent to Human Genome Sciences, Inc. ("HGS") based on HGS's Australian Patent Application Number 696764. I have read and understand the specification and claims of Australian Patent Application Number 696764.

3. I am aware that Associate Professor Peter Rogers of the Department of Obstetrics and Gynaecology, Monash University, Victoria, Australia has also been asked by the Ludwig Institute to serve as a scientific expert in this matter. I am aware that a Declaration by Associate Professor Rogers has been prepared.

4. I am aware that two Declarations by John Francis McCann of 31 Market Street, Sydney, New South Wales, have also been prepared in respect of this matter. I have read and understand the Declarations of John Francis McCann and the Exhibits thereto.

5. I have read and understand the Declaration by Associate Professor Rogers. I agree with the opinions expressed by Associate Professor Rogers in his declaration.

AND I MAKE this solemn declaration by virtue of the Statutory Declarations Act 1959, and subject to the penalties provided by that Act for the making of false statements in statutory declarations, conscientiously believing the statements contained in this declaration to be true in every particular.

DECLARED at Adelaide

this 16th day of February 2000

Francis John Ballard

BEFORE ME:

B. Dolman J.P. 17434

AUSTRALIA

Patents Act 1990

IN THE MATTER OF Australian Patent Application Serial No 696764 by Human Genome Sciences, Inc.

-and-

IN THE MATTER OF Opposition thereto by Ludwig Institute for Cancer Research

THIS IS Exhibit 1 referred to in the Statutory Declaration of Francis John Ballard made before me this 16th Day of February, 2000

B. Dalman, J.P. 17434

A Justice of the Peace for and for the State of South Australia

Abbreviated Curriculum Vitae, F.J. BALLARD, October 1999

1 NAME — Francis John BALLARD

2 BIRTH — 19 June 1940, Penang, Malaysia

3 QUALIFICATIONS

1961 BSc (Hons) (Univ. W.A)
1964 PhD (Univ. W.A)
1984 DSc (Univ. W.A)

4 PRESENT POSITIONS

Managing Director, GroPep Pty Ltd
Director and Chairman, PrimeGRO Pty Ltd
Affiliate Professor in Biotechnology, University of Adelaide

5 PREVIOUS APPOINTMENTS

1965-1966	Research Fellow, Temple University, USA
1966-1969	Assistant Professor of Biochemistry, Temple University, USA
1969-1971	Queen Elizabeth Fellow, CSIRO Nutritional Biochemistry
1971-1972	Senior Research Scientist, CSIRO Nutritional Biochemistry
1972-1977	Principal Research Scientist, CSIRO Nutritional Biochemistry
1977-1980	Senior Principal Research Scientist, CSIRO Human Nutrition
1986-1994	Chief Research Scientist, CSIRO Human Nutrition
1986-1991	Assistant Chief, CSIRO Human Nutrition
1991-1994	CEO, GroPep Pty Ltd
1991-1999	Director, CRC for Tissue Growth and Repair

6 RESEARCH HONOURS and AWARDS

1971	Mead Johnson Award for Research in Nutrition
1975	Edgeworth David Medal
1976	Boehringer Mannheim Medal
1978	David Rivett Medal
1980	LKB Medal
1984	Lemberg Medal
1997	Fellow, Australian Academy of Technological Sciences and Engineering

7 MEMBERSHIPS, COMMITTEES and OTHER ACTIVITIES

1972-1977	Secretary, Australian Biochemical Society
1979-1982	Chairman, Committee on Symposia, International Union of Biochemistry
1979-1985	Editorial Board, Journal of Development Physiology
1979-1994	SIDS Research Committee (SA)
1981-1991	Editorial Board, Proceedings of the Nutrition Society of Australia
1982-1984	President, Australian Biochemical Society
1982-1990	International Committee on Proteolysis
1983-1988	Editorial Board, Journal of Nutrition, Growth and Cancer
1983-1990	Editorial Board, Cell Biology and Toxicology
1983-present	Muscular Dystrophy Association (SA) Research Advisory Committee
1986-1990	Queen Victoria Hospital – Research Advisory Committee
1987-1990	President, Australian Perinatal Society
1988-1990	Bresatec Ltd – Research Advisory Committee
1990-1994	Child Health Research Institute – Research Advisory Committee
1994-present	Editorial Board, Biochemical Journal
1995-present	Editorial Board, International Journal of Biochemistry and Cell Biology
1999-present	Member, Australian Government Biotechnology Consultative

8 PUBLICATIONS Total Number = 290

KEY PAPERS

Ballard, F.J., Hanson, R.W and Kronfeld, D.S (1969) Carbohydrate and lipid metabolism in ruminants. *Fed.Proc. 28*, 218-231.

Philippidis, H., Hanson, R.W., Reshef, L., Hopgood, M.F. and **Ballard, F.J.** (1972) The initial synthesis of proteins during development. Phosphoenolpyruvate carboxykinase mRNA during glucose repression in liver. *Biochem. J.* **126**, 1127-1134.

Tilghman, S., Hanson, R.W., Reshef, L. Hopgood, M.F. and **Ballard, F.J.** (1974) Rapid loss of translatable phosphoenolpyruvate carboxykinase mRNA during glucose repression in liver. *Proc. Nat. Acad. Sci. US* **71**, 1304-1308.

Knowles, S.E and **Ballard, F.J.** (1976) Selective control of the degradation of normal and aberrant proteins in Reuber H35 hepatoma cells. *Biochem.J.* **156**, 609-617.

Gunn, J.M., Clark, M.G., Knowles, S.E., Hopgood, M.F and **Ballard, F.J.** (1977) Reduced rates of proteolysis in transformed cells. *Nature* **266**, 58-60

Ballard, F.J., Knowles, S.E., Wong, S.S.C., Bodner, J.B., Wood, C.M. and Gunn, J.M. (1980) Inhibition of protein breakdown in cultured cells is a consistent response to growth factors. *FEBS Lett.* **114**, 209-212.

Ballard, F.J., Francis, G.L., Ross, M., Bagley, C.J., May, B. and Wallace, J.C. (1987) Natural and synthetic forms of insulin-like growth factor-1 (IGF-1) and the potent derivative, destripeptide IGF-1: biological activities and receptor binding. *Biochem. Biophys. Res. Commun.* **149**, 398-404.

Hopgood, M.F., Knowles, S.E., Bond, J.S. and **Ballard, F.J** (1988) Degradation of native and modified forms of aldolase microinjected into HeLa cells. *Biochem.J.* **256**, 81-88.

Conlon, M.A., Tomas, F.M., Owens, P.C., Wallace, J.C. Howarth, G.S and **Ballard, F.J.** (1995) Long R^3 insulin-like growth factor-I (LR^3IGF-I) infusion stimulates organ growth but reduces IGF-I, IGF-II and IGF binding proteins in the guinea pig. *J. Endocrinol.* **146**, 247-253.

Belford, D.A., Rogers, M.L, Regester, G.O., Francis, G.L, Liepe, I.J., Priebe, I.K. and **Ballard, F.J.** (1995) Milk-derived growth factors as serum supplements for the growth of fibroblast and epithelial cells. *In vitro Cell. Dev. Biol. Anim.* **31**, 750-758.

9 TECHNOLOGY TRANSFER & COMMERCIALISATION

Patents:

Responsible for the preparation and responses to examiners worldwide for 12 patent families including the following ones as an inventor:

"Peptide analogues of mammalian IGF-I": PCT/AU86/00246
"Growth Factor": PCT/AU88/00485
"Method for treating intestinal diseases": PCT/AU91/00031
"Growth-promoting agent": PCT/AU91/00303
"Method of administering IGF-I, IGF-II and analogs thereof to birds": PCT/US93/08279
"Modified milk growth factor": PCT/AU95/00237
"Use of IGF in combination with insulin": PCT/AU95/00422
"Matrix binding factor": PCT/AU99/00292

Commercialisation:

Responsible for initiating, negotiating and finalising all R & D agreements, Licence agreements, and

AUSTRALIA

Patents Act 1990

IN THE MATTER OF Australian Patent Application Serial No 696764 by Human Genome Sciences, Inc.

-and-

IN THE MATTER OF Opposition thereto by Ludwig Institute for Cancer Research

STATUTORY DECLARATION

I, Kari Alitalo, a Research Professor of the Finnish Academy of Sciences, at The Molecular/Cancer Biology Laboratory, Biomedicum Helsinki, P.O.B. 63 (Haartmaninkatu 8) 00014 University of Helsinki, Finland, do solemnly and sincerely declare as follows:

Introduction

1.1 In February 2000 I executed a first statutory declaration (hereinafter referred to as "OKA1" (Opponents, Kari Alitalo, 1st Declaration)) to provide experimental evidence in support of the opposition filed by Ludwig Institute for Cancer Research ("Ludwig Institute") to the issuance of a patent to Human Genome Sciences, Inc., ("HGS") based on HGS's Australian Patent Application No. 696764 ("the opposed application"). That first declaration included a brief summary of my scientific credentials and an introduction in which I set forth some conventional terminology and relevant background information regarding VEGF-C and signal peptides.

1.2 The patent applicant HGS subsequently filed declarations from three scientists, Jennifer Ruth Gamble (hereinafter "AJG1"), Nicholas Kim Hayward ("ANH1"), and Stuart A. Aaronson ("ASA1"). Those declarations take issue with aspects of my first declaration. I note at the outset that HGS filed three additional declarations from three additional scientists (John Stanley Mattick ("AJM1"), Susan Power ("ASP1"), and Tom Rapoport

("ATR1")) that neglected to comment directly on the issues raised and/or experiments described in my first declaration. Therefore, my initial comments in response to HGS's declarations will be directed principally to the criticisms raised in AJG1, ANH1, and ASA1.

1.3 Second, Ludwig Institute also asked me to provide information regarding sequencing analysis of Human Genome Science's VEGF2[1] clone, deposited with the ATCC and referred to in the opposed application (as amended). That sequence analysis will provide helpful information for replying to issues raised by all of the declarants, but especially Dr. Power.

1.4 Third, Ludwig Institute asked me to comment on the relevance of certain experiments that Human Genome Sciences asked Dr. Susan Power to perform, and that were summarized in ASP1.

Reply to criticisms of my initial experiments and first declaration.

A. Initial observations about the weight of evidence.

2.1 I have reviewed all of the comments made in response to my first declaration. The criticisms regarding the experimental design and the data obtained as a result of my expression studies do not cause me to change my opinion as set forth in my first declaration. I note that AJG1, ANH1, and ASA1 fail to offer scientific data in support of their criticisms and fail to demonstrate that expression of VEGF2 according to the opposed application is feasible. Instead, the declarations recite potential shortcomings in the express teachings of the opposed application and potential remedies thereof (AJG1 at 6.5; ANH1 at 3.13-3.20; ASA1 at 16). If an objective scientist were to study all of the experimental evidence initially presented by the opponent and HGS in this opposition, the scientist would conclude that there is one set of experiments (reported in my first declaration) that VEGF2 as taught in the opposed application is not expressed and

[1] I note that the body of the specification of the opposed application refers to "VEGF2" whilst the claims and the HGS declarants refer to "VEGF-2". I assume that those terms are used in the opposed application and by the HGS declarants to refer to the same thing.

secreted, and no evidence whatsoever to the contrary. In any event, the further experiments conducted in my laboratory that I describe below provide still more evidence in support of the opponent's position.

2.2 Dr. Gamble criticized my first declaration by observing that I already knew, before conducting any experiments, that the 350 amino acid VEGF2 did not have a proper signal sequence. (AJGI at 7.41.) She is correct that by 1996 we had evidence that the relevant gene encoded a protein of 419 amino acids (not 350) and that the working signal peptide was from the part that was "missing" from the 350 amino acid VEGF2 sequence in the opposed application. If she thinks that this prior knowledge should have been used in my experimental design or that failure to do so represents a fault in the experimental design, then she misunderstands the purpose for my experiments. It is my understanding that the purpose of the opposition proceeding is to evaluate the merits of the HGS patent application, from the vantage point of early 1994, when it was filed. What I or anybody else knew in 1996 from my independent research should not confuse that inquiry, and certainly should not be credited to HGS. In fact the opposed patent application teaches a 350 amino acid VEGF2 and says that this sequence consists of a leader sequence of 24 amino acids and a mature sequence of about 326 amino acids. Since the patent application contained no experimental evidence whatsoever to support that assertion, I ran a set of experiments to see if it was correct or incorrect. The experiments showed that the patent application was wrong. Additional experiments, reported below, confirm that the opposed application was wrong.

B. My initial experiments were patterned from HGS's own teachings.

2.3 As explained in detail by Dr. Rogers in his first declaration, the opposed application taught an incomplete VEGF2 sequence lacking N-terminal amino acid sequences from the VEGF2 cDNA and protein. HGS filed a second application (Document D44, hereinafter referred to as "HGS II") in June 1995, which is not the subject of this opposition, but which is relevant because it pertains to a "full length" VEGF2 that is not missing the N-terminal sequences. Example 3 in HGS II provides a method for the expression of recombinant VEGF2 in COS cells. With the exception of the cell line, I generally followed the experimental design taught in Example 3 of HGS II in my first declaration. (For example, HGS II teaches to express VEGF2 with an HA tag fused in-frame to the 3'

end of VEGF2.) I used 293T cells for my expression studies since it was known at the time of the experimentation that the 293T cell line allows greater proteolytic processing and thus enables VEGF-C precursors a greater opportunity to become secreted. This phenomenon was, in fact, pointed out in each of the declarations (AJG1, Paragraph 7.45; ANH1, Paragraph 5.5; ASA1, Paragraph 10). If anything, the criticisms by Drs. Gamble, Hayward, and Aaronson of the experimental design and evidence supplied in my first declaration provides evidence that HGS II fails to teach a viable method for generating the VEGF2 protein. The Patent Office might wish to forward the criticisms provided by HGS's experts to the appropriate examiner handling the HGS II application in Australia.

2.4 Dr. Gamble, Dr. Hayward, and Dr. Aaronson all criticized my initial work for using an HA tag to make the VEGF2 construct. (See, e.g., AJG1 at 7.43 - 7.44; ANH1 at 5.3-5.4 and 5.6-5.10; and ASA1 at 7 - 13.) Use of the HA tag was allegedly taught in the opposed application (see, e.g., page 8, second full paragraph), and, as explained above, was explicitly taught in an Example of HGS II. If the HA tag causes any problems, then it reflects another defect in the teachings of the application and the teachings of HGS II. And, none of the scientists appears to believe that an HA tag causes any problems, according to other parts of their declarations. (See AJG1 at 7.45; ANH1 at 5.5; and ASA1 at 10.) In any event, I repeated the experiments for this declaration and used a VEGF-C antibody to precipitate both VEGF-C and VEGF2, thus answering the criticisms of Drs. Gamble and Hayward. As reported below, the VEGF2 taught in the patent application still was not expressed and secreted.

C. HGS Patent Application 714484 is irrelevant

2.5 In this paragraph I respond to similar allegations of Drs. Gamble, Hayward, and Aaronson, in which all three declarants attempt to obfuscate the problems in the opposed patent application by relying on information in a totally different patent application:

2.5.1 Dr. Gamble expressed the following opinion at AJG1 at 7.45:

> In HGS' Australian Patent No. 714484, a monoclonal anti-HA antibody was used to successfully immunoprecipitate VEGF-2 which had been modified to contain an HA epitope at its carboxy terminus. It is unclear

> to me why Dr. Alitalo apparently was not able to isolate VEGF-2 using a His tag at the C-terminus. One explanation may be the type of mammalian cell line used in the experiments . . . .

2.5.2 Dr. Hayward made similar declarations at ANH1 at 5.5:

> HGS scientists have reported the successful isolation of a modified VEGF-2 protein containing an HA tag at its carboxy terminus using a monoclonal anti-HA antibody. (See, HGS Australian Patent No. 714484 and Hu JS et al (1997) FASEB J May;11(6):498-504). These studies were conducted in COS cells, whereas the experiments set forth in Dr. Alitalo's declaration were conducted in 293T cells . . .

2.5.3 Dr. Aaronson made similar declarations at ASA1 at 10:

> The HGS scientists have reported the successful isolation of a modified VEGF-2 protein containing an HA-tag at its carboxy terminus using a monoclonal antibody to HA (See, HGS Australian Patent No. 714484 and Hu J.S. et al. FASEB J. 11 (6): 498-504). However, the HGS studies were conducted in COS cells, whereas Dr. Alitalo's experiments were conducted in 293T cells . . . .

2.6 As Drs. Gamble, Hayward, and Aaronson all know, the HGS patent document 714484 to which they refer is not the opposed application. Instead, document 714484 is the Australian version of the second application (HGS II) that HGS filed after they realized that the VEGF2 in the opposed application was incomplete.[2] Even if the HA tag was used successfully in an experiment in HGS II, that experiment related to 419 amino acid VEGF2, and not to the merits of the opposed application, which taught an incomplete VEGF2. The results reported in my first declaration for VEGF2 were negative because cells cannot express and secrete the incomplete VEGF2 molecule as taught by HGS. Dr.

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[2] The 1997 publication referred to by Dr. Hayward and Dr. Aaronson was published even later than HGS II was filed, and also relates to the 419 amino acid VEGF2.

Gamble and Dr. Hayward's speculation about cell lines is wrong, as shown in the additional experiments that I describe below.

D. Additional experiments to prove that VEGF2 cannot be expressed and secreted.

3.1 Ludwig Institute asked me to design and perform further protein expression studies that would address concerns raised by AJG1, ANH1, and ASA1 directed towards my first declaration. The following analyses of VEGF2 expression, proteolytic processing, and secretion profiles provide further support that the opposed application fails to teach a VEGF2 that can be expressed and secreted.

1. Background/Review

3.2. VEGF2 taught by HGS in the opposed application corresponds approximately to amino acids 70 to 419 of the human VEGF-C prepro-peptide. Like most complete protein coding sequences, the VEGF2 taught in the opposed application starts with a methionine. However, as analyzed by the SignalP program at Center for Biological Sequence Analysis, The Technical University of Denmark, this protein does not seem to contain a signal sequence (See OKA1 at 7.1). Among the approximately 70 amino acids that are missing from the N-terminus of VEGF2 in the opposed application are the initial approximately 31 amino acid residues that represent the VEGF-C signal sequence, responsible for directing secretion of the polypeptide.

2. Experimental Procedure

3.3 Cells and Plasmids:

3.3.1 A principal criticism from the HGS experts was the use of the 293T cell line rather than the COS cell line. Of course, nothing in the opposed application teaches that 293T cells should not be used.[3] However, in order to fairly evaluate the assertions

[3] Contrary to anything stated or implied by the HGS declarants, the opposed application has no working examples involving COS cells or other cells. The opposed application mentions COS cells among a list of exemplary cell lines at page 15.

made by HGS's experts, I performed parallel expression studies in both cell lines for this declaration. 293T and COS7 cells were grown in DMEM supplemented with 10% fetal bovine serum, glutamine and penicillin/streptomycin.

3.3.2 The polymerase chain reaction (PCR) was employed to construct a DNA fragment that corresponded to amino acids 70 to 419 of prepro-VEGF-C. Amino acid residues 70 to 419 of prepro-VEGF-C corresponds essentially to the full length sequence of the VEGF2 polypeptide described in the opposed application. Nucleotides 559 to 1608 of a VEGF-C cDNA (GenBank accession number X94216) were PCR amplified with the primers 5'-CGCGGATCCATGACTGTACTCTACCCA-3' containing a BamHI site and 5'-CGCTCTAGATCAAGCGTAGTCTGGGACGTCGTATGGGTACTCGAGGCTCATTTGTGGTCT-3' containing a XhoI site, HA-tag, a stop codon and a XbaI site. The PCR-amplified DNA was cloned into vector pcDNA1(Amp) (Invitrogen) and the resultant vector was designated as VEGF-2(HGS)/pcDNA1.

3.3.3 Also constructed was a VEGF-C/pcDNA1 construct to serve as a positive control for expression and secretion studies. The VEGF-C/pcDNA1 construct contains the full length (419 codon) cDNA sequence of VEGF-C.

3.4 Metabolic labelling:

3.4.1 To address the differences in expression, proteolytic processing, and secretion among cell lines, both 293T and COS cells were selected for the expression study. 293T or COS7 cells were transfected with either VEGF-2(HGS)/pcDNA1 or VEGF-C/pcDNA1. "Mock" transfected cells (transfected with "empty" vector) were used as a negative control.

3.4.2 Forty-eight hours after transfecting the cells with one or the other plasmid, the cells were washed twice with phosphate-buffered saline solution (PBS) and metabolically labeled in MEM medium containing 100 mCi/ml ^{35}S-methionine and ^{35}S-cysteine (Promix, Amersham) over night. The radioactive amino acids (^{35}S-methionine and ^{35}S-cysteine) were introduced into the cell growth medium to assist in the identification of expressed polypeptides in the extracellular medium

and in cell lysates. The cells used would incorporate these radioactive amino acids into nascent polypeptides during protein biosynthesis. The cell growth media after this overnight growth period is referred to as "conditioned media" because it has been conditioned by whatever polypeptides and other molecules the cells have secreted. After the overnight growth period, the conditioned media was harvested and cleared by centrifugation.

3.4.3 In addition to collecting the extracellular media to assay secreted proteins, the cells were lysed in order to assay proteins that were synthesized in the cells but not secreted. After washing for three times with ice cold PBS, the cells were lysed in ice cold RIPA-buffer (150 mM NaCl, 1% NP-40, 0.5% DOC, 0.1% SDS, 50 mM Tris) supplemented with 0.01 U/ml aprotinin, 1 mg/ml leupeptin and 1 mM PMSF, and the lysate was cleared by centrifugation. These latter ingredients were protease inhibitors, to prevent proteolytic degradation of proteins following the lysis step.

3.5 Immunoprecipitation:

Immunoprecipitation experiments were conducted to identify the presence of the various VEGF-C or VEGF2 polypeptides in the conditioned media or cell lysates.

3.5.1 For immunoprecipitation, the conditioned media from cell cultures were supplemented with BSA and Tween 20 to final concentrations of 0.5% and 0.02%, respectively. The different VEGF-C or VEGF2 peptides were immunoprecipitated with polyclonal antibodies raised against a synthetic peptide corresponding to amino acid residues 104-120 of the VEGF-C prepro-peptide (Antisera 882, reported in Document D71, Joukov *et al.*, 1997) at 4°C overnight. As an additional check for the presence of VEGF2 peptides, the conditioned medium and the lysates of the VEGF-2(HGS)/pcDNA1 or mock transfected COS7 cells were also immunoprecipitated with 1 mg/ml monoclonal anti-HA-antibodies (HA 11, BabCO).

3.5.2 The immunocomplexes were then precipitated with protein A-Sepharose and washed 2-3 times with 1 X binding buffer (0.5% BSA, 0.02% Tween20 in PBS)

and once with PBS at 4°C. The proteins were analyzed by SDS-PAGE in a 12.5% gel under reducing conditions.

3. Experimental Results

3.6 The immunoprecipitated proteins were analyzed by SDS-PAGE on a 12.5% gel under reducing conditions. An autoradiogram of the SDS-PAGE analyses is attached hereto as Exhibit 1.

3.6.1 293T cells (A) or COS7 cells (B and C) were transfected with expression vectors coding for VEGF2 (ie., VEGF-2(HGS)/pcDNA1) or VEGF-C (ie., VEGF-C/pcDNA1). When 293T or COS7 cells are transfected with the VEGF-2(HGS)/pcDNA1 construct, no VEGF2 protein can be detected in the conditioned medium (Exhibit 1, panel A and B, lane 1). These lanes look very much like the "mock" transfected controls in lane 3. Several polypeptides expressed from the VEGF-C/pcDNA1 construct were identified (Exhibit 1, panel A and B, lane 2). The dark band of approximately 30kDa corresponds to a processed form of VEGF-C in which the C-terminal propeptide has been cleaved off. The approximately 21kDa band represents the fully processed form of VEGF-C from which both N- and C-terminal propeptides have been removed. As previously reported, the processing of VEGF-C was less efficient in COS7 cells (Exhibit 1, panel B, lane 2) than in 293T cells (Exhibit 1, panel A, lane 2) (See Document D71, Joukov *et al., EMBO J., 16*: 38998-3911(1997)).

3.6.2 The conditioned media and the cell lysates of the COS7 cells transfected with VEGF-2(HGS)/pcDNA1 construct or empty vector ("mock") were also subjected to immunoprecipitation with monoclonal anti-HA antibodies, but no VEGF2 polypeptides could be detected when the immunoprecipitates were analysed by SDS-PAGE (Exhibit 1, panel C).

4. Conclusions

3.7 VEGF-2 as taught in the opposed application cannot be produced as an expressed and secreted protein. This is evident from the inability of VEGF2 as taught in the opposed application to be immunoprecipitated from conditioned media of either COS cells or 293T

cells. Taking into consideration what is now known about the gene corresponding to VEGF2, it is clear that one reason for this defect is that VEGF2 taught in the opposed application lacks a signal peptide, so it is not secreted. The experiments reported herein also rebut the inference by Dr Rapoport (ATR1 at 15) that residues 70-419 of VEGF2 provide sufficient information for expression, proper processing and secretion.

3.8 We now know that when cells express the full length prepro-VEGF-C, they secrete the resultant protein, which is proteolytically processed. This observation was confirmed by these experiments: as expected, VEGF-C protein products are readily detected in conditioned media from both 293T and COS7 cell lines that were transfected with the full length VEGF-C construct.

3.9 Even though VEGF2 as taught in the opposed application lacks a signal peptide to direct its secretion, we now know that VEGF2 is not really an intracellular protein, either. Since VEGF2 is not a normal intracellular protein, it is likely rapidly degraded in cells, if the truncated protein is synthesized at all. Ineffective production and rapid degradation are two possible explanations why no VEGF2 peptides were detectable in cell lysates of cultured cells transfected with VEGF-2(HGS)/pcDNA1.

3.10 The results of these experiments completely confirm and validate the experiments described in my first declaration, namely, that the 350 amino acid VEGF2 taught by HGS in the opposed application cannot be expressed and secreted as described in the opposed application because it lacks a true signal peptide.

3.11 The results of these experiments eliminate any criticism that the cell lines used for expression influenced the results. VEGF2 as taught in the opposed application cannot be expressed and secreted in either COS cells or 293T cells, whereas full length prepro-VEGF-C can be expressed and secreted in either cell type.

3.12 The results of these experiments eliminate any criticism that the antibody used for identification of polypeptides affected results, because an identical antisera was used for VEGF2 and VEGF-C. The polyclonal antisera raised against amino acids 104-120 of prepro-VEGF-C would have recognized either polypeptide (if it were present) because the recognition sequence for the antisera is present in both the VEGF-C and the VEGF2

sequence. (The results with the anti-HA tag antibody serve only to confirm that VEGF2 as taught in the opposed application is defective for expression and secretion.)

Sequencing the VEGF2 clone that HGS deposited with the ATCC

4.1 The opposed application was originally filed with a blank reference to a deposit with the American Type Culture Collection, which HGS eventually amended to specify ATCC Accession Number 75698, deposited 4 March 1994. (See page 5.) The application also states that the sequence of the polynucleotides contained in the deposited materials are controlling in the event of any conflict with the description of the sequence in the application. (See page 9.) Many of HGS's declarants have made representations concerning what the HGS application would allegedly have taught them, and the nature of the deposited clone is important for assessing the validity of their declarations, as I discuss below and as Drs. Rogers and Ballard also discuss.

4.2 My laboratory obtained a sample of ATCC clone 75698 directly from the ATCC. I attach hereto as Exhibit 2 a copy of original paperwork from the ATCC that accompanied the clone that was shipped to me. My laboratory sequenced the clone using standard laboratory techniques.

4.3 The VEGF2 sequence of ATCC clone 75698 begins as follows . . . .

```
        10                  30                  50
ggcacgagcAGAGAACAGGCCAACCTCAACTCAAGGACAGAAGAGACTATAAAATTTGCT
          R  E  Q  A  N  L  N  S  R  T  E  E  T  I  K  F  A
```

I have distinguished the parts of the clone that do not correspond with VEGF2 sequence using lower case letters. (This sequence presumably corresponds to sequence from the cloning vector in which the VEGF2 cDNA was inserted when deposited with the ATCC). A comparison between the sequence of the deposit and the VEGF2 sequence in Figure 1 of the opposed patent application shows that the deposited VEGF2 begins with nucleotide 142 or 143 in Figure 1. The first VEGF2 amino acids encoded by the deposited VEGF2 clone are REQANL . . . ., i.e., the clone begins with position 25 of the approximately 350 amino acid VEGF2 in the patent application. In other words, the HGS scientists deposited a cDNA that contained only *the mature* (as taught in the opposed application) VEGF2 of about 326 codons, as taught in the opposed application. The HGS scientists failed to deposit a VEGF2 containing the first approximately 24 codons, which they taught were the leader sequence of VEGF2. (And, compared to the true 419 amino acid VEGF2 taught in the HGS II application, above 93 amino acids are missing from the deposit.)

Reply to Susan Power's Declaration

5.1 Perhaps in response to my first declaration in which I demonstrated that VEGF2 cannot be expressed and secreted as taught in the opposed application, HGS filed a declaration of Susan Power (ASP1) in which she describes some expression experiments of her own. Other HGS declarants speak approvingly of Dr. Power's experiments. (See, e.g., ASA1 at 15 - 22.) This section of my declaration provides an analysis of Dr. Power's experimental work as it relates to the opposed application.

5.2 Dr. Power describes her instructions from HGS as follows: "The Patent Attorneys for Human Genome Sciences (HGS) requested that I perform the following experiments in order to determine whether the 350 amino acid form of VEGF-2 (corresponding to residues 70 to 419 of the 419 amino acid form of VEGF-2) fused in frame with a heterologous signal sequence would result in the expression and secretion of the protein from eukaryotic cells." ASP1 at 2. She was not instructed to repeat any particular teachings in the opposed application, or to use materials or methods described in the application.

5.3 The experiments that HGS asked Dr. Powers to perform may be an interesting scientific curiosity, but they have nothing to do with the teachings in the opposed patent.

application. The opposed application teaches the reader that the VEGF2 of about 350 amino acids *already* consists of a leader sequence (i.e., a signal sequence) representing the first approximately 24 amino acids, and a mature protein of 326 amino acids. (See, e.g., page 5 of opposed application; see also OKA1 at 2.1 - 3.3.) However, HGS apparently did not ask her to run such an experiment, or to report the results of such an experiment if she ran it.[4] Scientists in 1994 or today would not have had any reason to express a protein that already contained a signal sequence using a method that involved attaching a second, heterologous signal sequence (e.g., Dr. Power's Ig Kappa signal sequence) to the beginning of the natural signal sequence. Therefore, it is not clear to me what basis there is in the patent application for instructing Dr. Power to attach a heterologous signal sequence to 350 amino acid VEGF2. Dr. Power's experiments are not a replication of any example in the opposed application or a reasonable extension of any of its teachings. Dr. Power was not asked to practice the teachings in the application, but rather, to use her present knowledge to design experiments unrelated to the patent application, using materials and methods that were available in 1994.

5.4 Dr. Powers states that, for starting materials, she used nucleotide sequences obtained directly from the ATCC and says that ATCC Deposit No. 75698 contains the nucleotide sequence encoding the 350 amino acid form of VEGF2. See ASP1 at 5. I find this statement very confusing because, as I indicated above, this ATCC clone does not encode 350 amino acids. Perhaps HGS supplied Dr. Power with the 350 amino acid form of VEGF2, and mistakenly led her to believe that the clone was the same as the deposit. The fact that the ATCC clone does not even contain the first twenty-four amino acids further confirms that HGS considered those amino acids to be the signal peptide, and thought that those amino acids should be removed. The opposed application did not teach to attach a foreign signal sequence to the 350 amino acid sequence.

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[4] As I report herein and in OKA1, I have run that experiment and shown that the teachings in the opposed application are wrong.

5.5 Dr. Power describes the antibody she uses as one "which recognizes the precursor form and the processed form of VEGF2." ASP1 at 3 and 13. This statement is confusing because it is unclear what "precursor" and "processed" refer to. For example, we know from experiments in our laboratory that the 419 amino acid prepro-VEGF-C (the precursor) is processed by removal of a signal peptide, removal of a large C-terminal BR3P domain representing almost half of the protein, and, to produce a fully processed VEGF-C, removal of still another N-terminal pro-peptide. See Document D71. Neither of HGS's patent applications relating to VEGF2 teach such processing. The opposed application teaches that VEGF2 is a 350 amino acid precursor with a 326 amino acid mature protein. As we now know that is not correct. Dr. Power further confuses this issue by adding an Ig Kappa signal peptide to the 350 amino acid VEGF2.

5.6 Dr. Power summarizes the results of her experiments in paragraph 15. As I explain above, this should be ignored, because the experiments that she ran are unrelated to the teachings in the patent application. One additional observation regarding her results is that she makes specific mention of a doublet of approximately 30 kDa being present in the medium from the cells. It is worth noting that the opposed application makes no mention of this species of polypeptide, or of a method of making it, or that one should expect to achieve it.

Summary

6.1 The experiments that I report herein confirm my first set of experiments (reported in OKA1) and establish that VEGF2 as taught in the opposed application cannot be expressed and secreted. None of the declarations filed by HGS provide any experimental evidence to refute this fact. To the extent that the HGS declarations offered any criticisms of my first set of experiments (legitimate or otherwise), I have addressed them in my second set of experiments. To the extent that the HGS declarations (e.g., Dr. Power) offer any experimental evidence, such evidence is irrelevant because it is not based on teachings in the opposed patent application.

AND I MAKE this solemn declaration by virtue of the Statutory Declarations Act 1959, and subject to the penalties provided by that Act for the making of false statements in statutory declarations, conscientiously believing the statements contained in this declaration to be true in every particular.

DECLARED at Helsinki

this 24th day of September 2001

Kari Alitalo

BEFORE ME:

(Signature of Witness)

JUKKA HEIKKILÄ
Notary Public

AUSTRALIA

Patents Act 1990

IN THE MATTER OF Australian Patent Application Serial No 696764 by Human Genome Sciences, Inc.

-and-

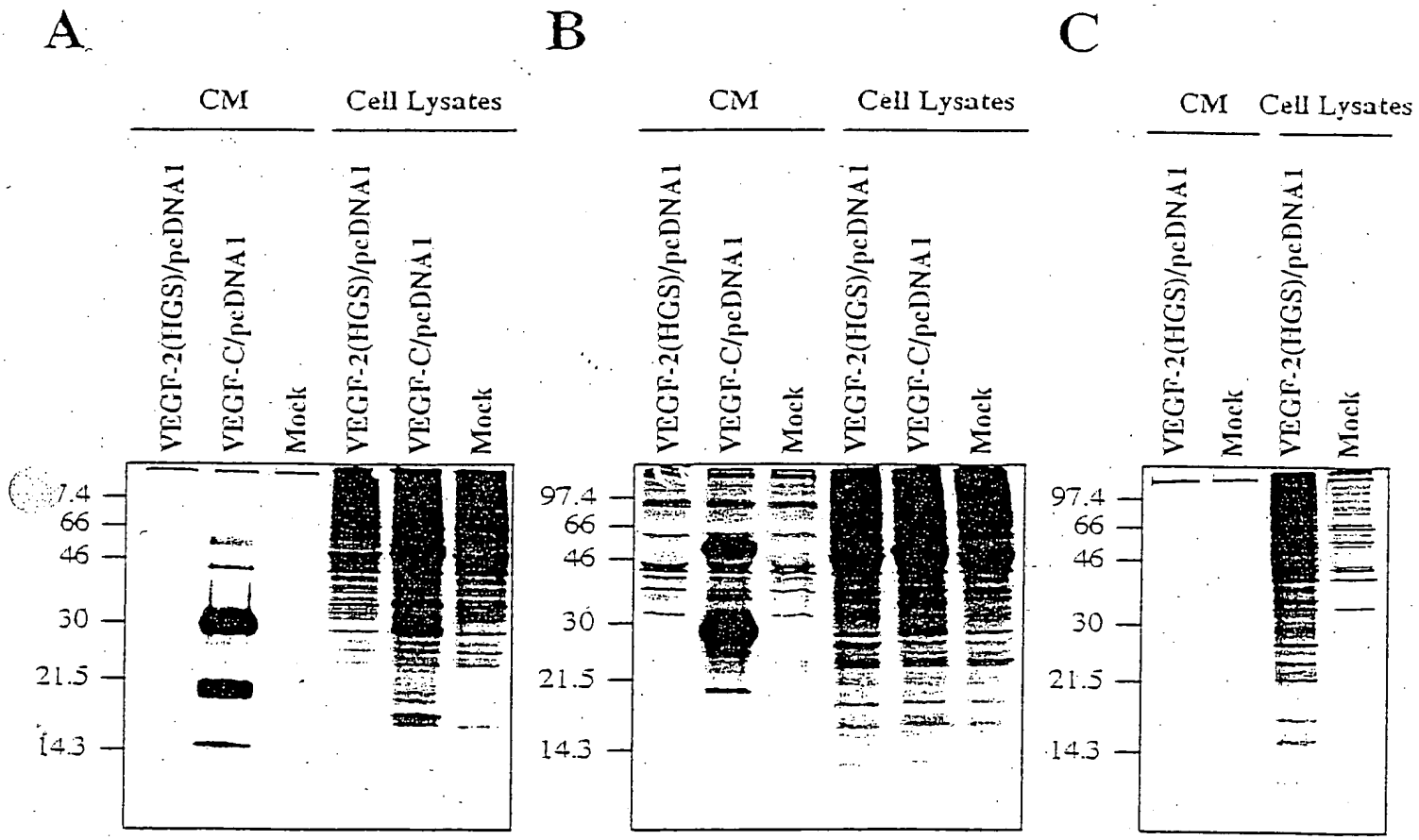
IN THE MATTER OF Opposition thereto by Ludwig Institute for Cancer Research

THIS IS Exhibit 1 referred to in the Statutory Declaration of Kari Alitalo made before me

DATED this 24th Day of September, 2001

.....

Witness JUKKA HEIKKILÄ
Notary Public


A
CM
Cell Lysates
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VEGF-C/pcDNA1
Mock
VEGF-2(HGS)/pcDNA1
VEGF-C/pcDNA1
Mock
97.4
66
46
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Cell Lysates
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VEGF-C/pcDNA1
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